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Disorders of the Endocrine System and of Metabolism

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Burket's Oral Medicine, Thirteenth Edition. Edited by Michael Glick, Martin S. Greenberg, Peter B. Lockhart, and Stephen J. Challacombe.
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ENDOCRINE DISEASES

The term "endocrine" was coined by Starling to contrast the actions of hormones secreted internally (hence *endo*crine) from those substances that are secreted onto external surfaces (exocrine, e.g., sweat or saliva).[1] The term "hormone" is derived from the Greek *hormân*, "to set in motion, stimulate," a derivative of *hormé* meaning "impetus" or "impulse." This describes well the dynamic actions of hormones and their ability to induce cellular responses and their regulation of the major physiologic processes of growth, reproduction, metabolism, and the maintenance of homeostasis (e.g., glucose and calcium). The release and actions of hormones are controlled by means of predominantly negative "feedback loops," as exemplified by the hypothalamus-pituitary-adrenal (HPA) axis (see Figure 22-1).

The most common endocrine disorders are (Figure 22-2):[2]

- Diabetes mellitus.
- Obesity.
- Thyroid disorders: hypothyroidism, hyperthyroidism, goiter.
- Menstrual disorders and/or hirsutism, usually due to polycystic ovarian syndrome (PCOS).
- Hypogonadism (in association with erectile dysfunction).
- Osteoporosis and metabolic bone disease.
- Subfertility (delay or difficulty in conceiving).
- Disorders of growth or puberty.

Endocrine disorders (the "endocrinopathies") are common, and are increasing in frequency. They encompass some of most prevalent of the chronic diseases, including diabetes mellitus[3] and increasingly obesity.[4,5] Endocrine diseases affect the entire system of endocrine glands, the hormones, synthesized and secreted by these glands, and the target organs that are susceptible to the effects of these hormones. Endocrine disorders are complex and their diagnosis is complicated by four interacting components:[6,7]

- The *hypothalamus* (Figure 22-3) contains most of the "sensing" organs and tissues, and is the part of the brain that monitors crucial determinants of homeostasis; that is, water, electrolyte and osmotic balance, metabolism, the fed and fasted state, and the stress response. Additionally, over the course of a lifetime, conception, pregnancy, growth, development, sexual maturation, and senescence are also regulated by the hypothalamus. Various "biologic clocks" exist that are linked into and exert control over the 24-hour circadian rhythm, the 28-day menstrual cycle, and the longer temporal cycles associated with growth, development, and sexual maturation, including as an example the timing of the onset of puberty. The hypothalamus most significantly is the link between the endocrine and nervous systems. The hypothalamus produces releasing and inhibiting factors that control the hormones of the pituitary, as well as other hormones throughout the body, via the pituitary—the second major component of the endocrine system.
- The *pituitary* is a small pea-sized endocrine gland that regulates all of the major endocrine glands located throughout the body. It does this by the release of trophic hormones that stimulate the growth of the other endocrine glands, or by the release of hormones that stimulate the endocrine glands to release the hormones synthesized

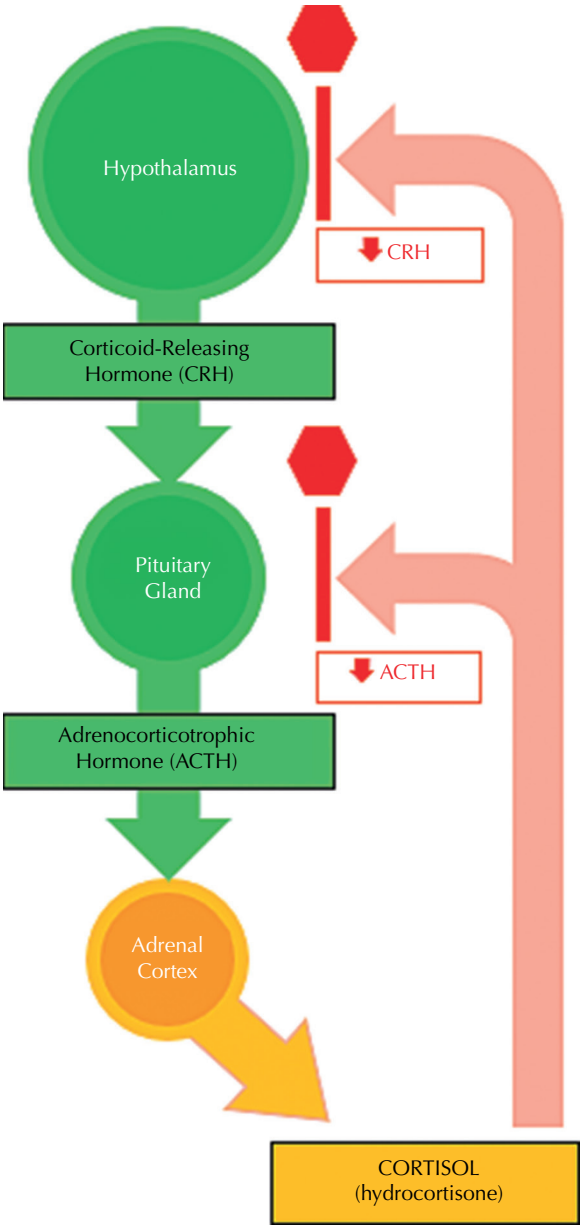


Figure 22-1 The hypothalamus-pituitary-adrenal (HPA) axis is an example of negative feedback inhibition. As the cortisol levels rise, the cortisol induces the hypothalamus to make less corticoid-releasing hormone, so causing the pituitary to make less adrenocorticotrophic hormone, which in turn causes the adrenal gland to produce less cortisol (the reverse applies: a lower cortisol level induces a rise in cortisol production). Courtesy of Mark Schifter.

within that gland itself. Except for oxytocin, all the hormones released by the major endocrine glands are under negative feedback control (meaning that the presence of circulating hormone downregulates further production of that hormone).

- *Major endocrine glands* includes the bilobed thyroid, the four parathyroid glands, the paired adrenal glands (sited atop the kidneys), the endocrine pancreas, and the gonads, testes, and ovaries). These glands synthesize and release the hormones that have the major effects on metabolism, water and electrolyte balance, glucose and calcium homeostasis, the stress response, as well as conception, growth, and development.
- *Hormones* are a class of signaling molecules, produced by endocrine glands that are generally transported by the circulatory system to target organs to regulate physiology and behavior (Box 22-1). Hormone production and function is complex, and includes biosynthesis and storage of a particular hormone in a particular gland, secretion (on receipt of the correct signal—often another hormone—by the gland), transport to the target cells/tissues, and recognition of the hormone by the target cell, via hormonal binding to a cell surface or intracellular receptor, resulting in transmission and amplification of the hormonal signal. The last stage is breakdown of the hormone.

In essence, it is either deficiencies or excess of these hormones of the major endocrine glands that result in significant disease states.[8] Malignancies of the endocrine glands are rare. There are a number of key aspects of endocrine disease about which dentists need to know:

- *Pathophysiology and management of the various endocrine diseases*. This ensures the safe delivery of dental care, the ability to possibly prevent disease progression or worsening morbidity, and to avoid serious potentially life-threatening complications of the patient's disease.
- *Complications that can arise from undiagnosed or poorly managed endocrine disease*. This includes knowledge of potentially life-threatening medical emergencies and the subsequent need to alter treatment planning (including awareness of potential drug interactions) or implement additional measures and resources so as to prevent the likelihood of such emergencies from occurring.
- *Manifestations of the disease in/on the stomatognathic system*. Recognition of the stomatognathic manifestations of endocrine disease is needed for the diagnosis of such conditions and also to identify those patients with poorly controlled or undiagnosed disease.

Hormones

There are five major classes of hormones (classified by their molecular weight and size and their precursor substrates; see Table 22-1),[9] and their function can be broadly classified into three areas of physiologic activity: growth and differentiation; maintenance of homeostasis; and reproduction.

Hormone release is the end-product of a long cascade of intracellular events. Polypeptide hormones, for example, require neural or endocrine stimulation of the cell to initiate

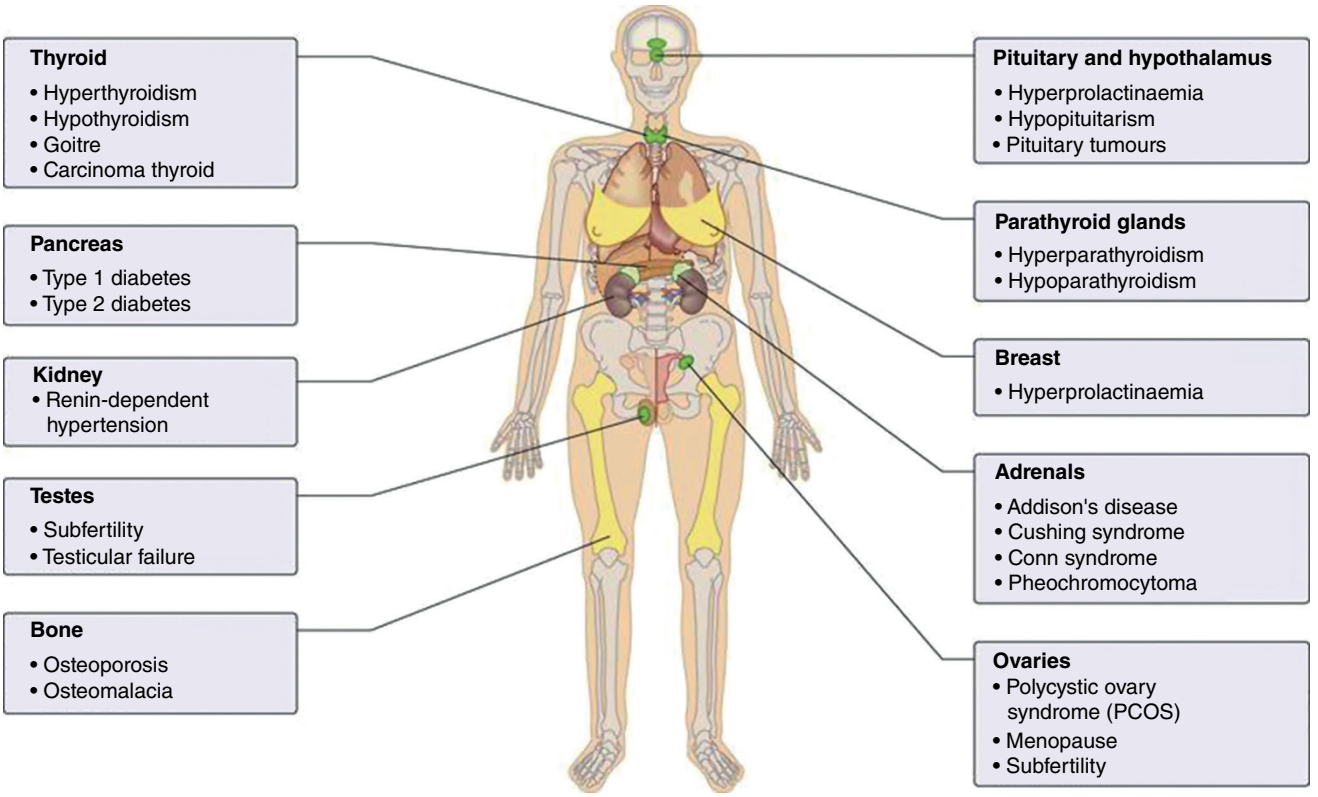


Figure 22-2 The major endocrine organs and common endocrine problems. *Source:* Kumar PJ, Clark ML (Eds.). *Kumar and Clark's Clinical Medicine*, 9th edn. Edinburgh: Saunders; 2017. Reproduced with permission.

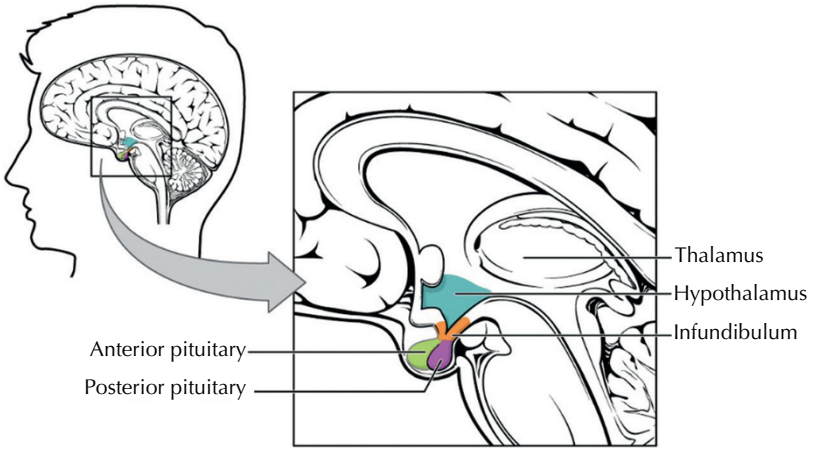


Figure 22-3 Hypothalamus and pituitary in detail. *Source:* Betts JG, Young KA, Wise JA, et al. *Anatomy and Physiology*. Houston, TX: OpenStax; 2013. https://openstax.org/books/anatomy-and-physiology/pages/1-introduction. Creative Commons Attribution License 4.0 license.

transcription from DNA to a specific messenger RNA (mRNA) and subsequent translation into a polypeptide product. This product is often a precursor molecule or "prohormone" that is biologically inactive, and is then further processed and packaged into granules, in the Golgi apparatus. These granules are transported to the plasma membrane before release, which is itself regulated by a complex combination of intracellular regulators.

Hormone secretion can be (1) *continuous*, as seen with the thyroid hormones, with a half-life of 7–10 days for T4 and 6–10 hours for T3, and with little variation in levels over the day, month, and year; or (2) *pulsatile*, which is the normal pattern for the gonadotrophins—that is, luteinizing hormone (LH) and follicle-stimulating hormone (FSH)—with a large amount of hormone released in a pulse every 1–2 hours, depending on the phase of the menstrual cycle. Growth hormone (GH) is also secreted in a pulsatile fashion, but with undetectable levels between pulses.

There are major factors that control the release of various hormones over days, for example the circadian rhythm,

weeks, and months, and in the case of the growth and sex hormones over years.[10] The menstrual cycle is an example of a longer and more complex (28-day) biologic rhythm.[11] Other regulatory factors include physiologic "stress" and acute illness, which produce rapid increases in adrenocorticotropic hormone (ACTH) and cortisol, GH, prolactin, epinephrine, and norepinephrine. Over the course of the sleep–wake cycle the secretion of GH and prolactin is increased, especially during the rapid eye movement (REM) phase of sleep. Food intake results in many hormones being released to regulate the body's control of energy intake and expenditure, and these are therefore profoundly influenced by feeding and fasting. Secretion of insulin is increased, while testosterone and GH are decreased after ingestion of food, and secretion of a number of hormones is altered during prolonged food deprivation.

Most hormones are secreted directly into the circulation from the endocrine glands. In contrast to this, the hormones released from the hypothalamus are excreted at much higher concentrations and are confined to the pituitary portal system. Many hormones are bound to proteins within the circulation—it is important to note that only the free (unbound) hormone is available to the tissues and is biologically active. This binding to the plasma proteins serves to buffer against very rapid changes in plasma levels of the hormone and additionally plays a role in regulation of hormonal activity. Many of the tests of endocrine function measure the total rather than the free hormone, giving rise to difficulties in interpretation when the binding proteins are altered in disease states or by drugs. Binding proteins comprise both specific, high-affinity proteins of limited capacity, such as thyroxine-binding globulin (TBG), cortisol-binding globulin (CBG), sex-hormone-binding globulin (SHBG) and insulin-like growth factor (IGF)-binding proteins (e.g., IGF-BP3); and other, less specific,, low-affinity protein carriers, such as prealbumin and albumin.

Box 22-1 Signaling by the Endocrine System

The endocrine system is an information signal system like the nervous system, yet its effects and mechanisms are clearly different. The endocrine system's effects are slow to initiate, and prolonged in their response, lasting from a few hours up to weeks.

- Endocrine signaling relies on hormones that usually travel far via the circulatory system to reach their target organ.
- Paracrine signaling is a form of cell–cell communication in which a cell produces a signal to induce changes in nearby cells, altering the behavior or differentiation of those cells. Paracrine factors diffuse over only a relatively short distance (locally active), in contrast to hormones.
- Autocrine cell signaling entails the cell secreting a hormone or chemical messenger that binds to autocrine receptors *on that same cell*, leading to changes in the cell.

Table 22-1 Major classes of hormones.

Class		Examples	Receptor Types
1	Small neuropeptides	• Gonadotropin-releasing hormone • Thyrotropin-releasing hormone • Somatostatin • Vasopressin	
2	Amino acid derivatives	Catecholamines: • Epinephrine (adrenaline) • Norepinephrine (noradrenaline) • Dopamine • Thyroid hormone	• Interact with cell surface membrane receptors[#]
3	Large proteins[*]	• Insulin • Luteinizing hormone • Parathyroid hormone	
4	Steroid hormones[†]	• Cortisol • Estrogen	• Interact with intranuclear receptors
5	Vitamin derivatives	• Retinoids (vitamin A derivatives) • Vitamin D	• Lipid soluble

[*] Released by the "classic" endocrine glands: pituitary, thyroid, parathyroid, pancreatic islet cells, adrenals, and gonads.
[†] Synthesized from cholesterol-based precursors.
[#] An exception is thyroid hormones, which act via cytoplasmic receptors.

Hormone Receptors

These are broadly divided as follows:

- *Cell surface or membrane receptors*: typically, transmembrane receptors that contain hydrophobic sections spanning the lipid-rich plasma membrane and trigger internal cellular messengers.
- *Nuclear receptors*: these typically bind hormones and translocate them to the nucleus, where they bind hormone-response elements of nuclear DNA via characteristic amino acid sequences (so-called zinc fingers). Abnormalities of hormone receptors can be a rare cause of endocrine disease. The activation of intracellular kinases, phosphorylation, release of intracellular calcium and other "second messenger" pathways, and the direct stimulation of DNA transcription result in some or all of the following:
  - Stimulation or release of preformed hormone from storage granules.
  - Stimulation or synthesis of hormone and other cellular components.
  - Opening or closing of ion (e.g., calcium channels) or water channels (e.g., aquaporin water channels).
  - Activation or deactivation of other DNA-binding proteins, leading to stimulation or inhibition of DNA transcription.

The sensitivity and/or number of receptors for a hormone can be decreased after prolonged exposure to a high hormone concentration (downregulation). Equally, the reverse is true when stimulation is absent or minimal: the receptors are increased in number and/or sensitivity (upregulation).

Primary and Secondary Endocrine Gland Failure

Primary endocrine gland failure occurs when there is dysfunction or removal of the specific end-organ endocrine gland—the thyroid, parathyroid, endocrine pancreas, adrenal glands, or gonads (ovaries and testes). Causes of primary endocrine gland dysfunction or destruction include autoimmune disease, atrophic change, inflammatory or neoplastic infiltration, or complications related to treatment, such as radiotherapy or surgical removal of the gland.

Secondary disorders of the same endocrine axes are caused by diseases of the pituitary gland. The key to diagnosing the site of the disease, either primary or secondary, requires understanding of the negative feedback control system so as to correctly interpret blood tests used in the investigation of endocrine diseases. Primary hormone deficiency due to a disease process of the endocrine end-organ (e.g., thyroid, adrenal, or gonad) will lead to a loss of negative feedback and subsequent elevation in the corresponding anterior pituitary trophic (stimulating) hormone. In secondary gland failure, there will be low or "inappropriately normal" levels of the pituitary trophic hormone in the presence of low end-organ hormone levels; for example, if a patient has low circulating free T3 (fT3) and T4 levels in the context of low thyroid-stimulating hormone (TSH) levels, then the site of the disease is likely to be in or of the pituitary gland.

Investigations of Endocrine Function[12]

See Table 22-2.

Basal Blood Level

Basal hormone levels are especially useful for systems with long half-lives (e.g., T4 and T3, insulin-like growth factor-1 [IGF-1], androstenedione, SHBG) that vary little over the short term and so samples taken at any specific time are satisfactory.

For those hormones that fluctuate in accordance with the circadian rhythm (e.g., testosterone and cortisol), measurements must be taken at an appropriate time of day, which is 11:00 am for testosterone, while the patient is fasted, and between 8:00 and 11:00 am for cortisol, also with the patient fasted. LH/FSH, estrogen, and progesterone vary with time of menstrual cycle, and renin/aldosterone may vary with sodium intake, posture, and age.

Measurement of stress-related hormones (e.g., catecholamines, prolactin, GH, and cortisol) can be problematic, as the patient may be stressed by their attendance at the hospital or by the venipuncture itself, leading to falsely high levels. Sampling via an indwelling cannula at some time after the initial venipuncture overcomes this problem.

Urine Collection

This is done over the course of 24 hours and has the advantage of providing an "integrated mean" of a day's secretion of select hormones, namely the catecholamines and cortisol. However, in practice these results are often complicated by poor patient compliance and incomplete/wrongly timed collection. Age, sex, and weight of the patient are also confounding factors.

Saliva

Salivary analysis has the advantage of avoidance of venipuncture, and is being increasingly used, especially in children (for steroid estimations) or for samples collected at home.[13,14]

Stimulation and Suppression Tests

In general, stimulation tests are used to confirm suspected deficiency, and suppression tests to confirm suspected excessive levels of hormone secretion. These tests are valuable in instances when the secretory capacity of a gland is damaged,

Table 22-2 Diagnosis of endocrine disorders.

Gland/Disease	Hormonal Problem	Diagnostic Assays/Investigations
Acromegaly	Growth hormone (GH) excess	• Plasma GH • Plasma insulin-like growth factor-1
Hyperprolactinemia	Prolactin excess	• Plasma prolactin
Adrenal		
Cushing's syndrome	Excess cortisol	• 24 h urinary free cortisol • 1 mg dexamethasone suppression test • Midnight serum or salivary cortisol
Addison's disease	Low cortisol (and aldosterone)	• Adrenocorticotropic hormone stimulation test
Aldosteronism	Excess aldosterone	• Plasma renin activity • Plasma aldosterone after saline infusion
Pheochromocytoma	Excess epinephrine and/or norepinephrine	• Plasma catecholamines • 24 h urinary catecholamines
Thyroid		
Hyperthyroidism	Excess T4 and/or T3	• Suppressed thyroid-stimulating hormone (TSH; most sensitive test)
Hypothyroidism	Low T4 and/or T3	• Elevated TSH (most sensitive test)
Gonadal Failure/Diseases		
Male—hypogonadism	Low serum testosterone	• Low serum free testosterone levels
Female—ovarian failure	Loss of ovarian estradiol	• Elevated serum gonadotropins (follicle-stimulating hormone and luteinizing hormone)

such that despite maximal stimulation by the trophic hormone, there is diminished output of primary hormone. For example, with the short ACTH stimulation test for adrenal reserve, the healthy subject shows a normal response, while the subject with primary hypoadrenalism (Addison's disease) demonstrates an impaired cortisol response to the injection of cosyntropin (Synacthen®, Mallinckrodt, Dublin, Ireland), a potent ACTH analogue.[15]

Causes of Endocrine Disease

Endocrine diseases can be divided into two major disease states: hormone excess and hormone deficiency (Table 22-3).[16] Hormone resistance can be considered as a separate and distinct third condition,[17] but in practice the effect is one of hormone deficiency.

Hormone Excess

Hormone excess can be caused by autoimmune disorders, the excess therapeutic administration of hormones, or autonomous release with tumors, as can be seen with benign adenomas of the parathyroid, pituitary, and adrenal glands.

Hormone Deficiency

The commonest cause of hormone deficiency is from glandular destruction by autoimmune diseases (Table 22-4) and iatrogenic causes, namely surgery and radiotherapy. Rare cases include infection, inflammation, infarction, hemorrhage, or tumor infiltration. Autoimmune-mediated damage is highly prevalent, as seen with Hashimoto's thyroiditis and that of the pancreatic islet β cells in type 1 diabetes mellitus (T1DM).

Hormone Resistance

Hormone resistance results in a disease state that is similar to that seen with hormone deficiency, but diagnosis is more difficult and complicated as there are usually normal levels of the hormone on testing. The more severe hormone resistance disorders are due to inherited defects in membrane receptors, nuclear receptors, or the pathways that transduce receptor signals. These disorders are characterized by defective hormone action despite the presence of increased hormone levels. The most prevalent acquired forms of functional hormone resistance include insulin resistance in type 2 diabetes mellitus (T2DM) and leptin resistance in obesity.[8,18]

Table 22-3 Endocrine disorders.

Hormone Excess	Examples
Neoplastic	
Benign	• Pituitary adenomas • Hyperparathyroidism • Thyroid nodules (autonomous) • Adrenal nodules (autonomous) • Pheochromocytoma
Malignant	• Adrenal cancer • Medullary thyroid cancer • Carcinoid tumors*
Multiple endocrine neoplasia (MEN)	• MEN1 • MEN2
Autoimmune	• Graves' disease
Iatrogenic	• Cushing's syndrome (excess corticosteroid administration)
Infections/inflammatory	• Subacute thyroiditis
Receptor mutations (for activation)	• Luteinizing hormone (LH) • Thyroid-stimulating hormone • Parathyroid hormone (PTH) receptors
Hypofunction (Hormone Deficiency)	
Autoimmune	• Hashimoto's thyroiditis • Type 1 diabetes mellitus • Addison's disease
Iatrogenic	• Radiation induced • Hypopituitarism • Hypothyroidism
Infectious/inflammatory	• Sarcoidosis of the hypothalamus
Hormone mutations	• Growth hormone (GH) • LH • Follicle-stimulating hormone (FSH) • Vasopressin
Enzyme defects	• 21-Hydroxylase deficiency (congenital adrenal hyperplasia)
Developmental defects	• Turner's syndrome (females)
Nutritional (vitamin) deficiency	• Vitamin D • Iodine
Hemorrhage/Infarction	• Adrenal insufficiency
Hormone Resistance	
Receptor mutations	
Membrane	• GH • Vasopressin • LH • FSH • Adrenocorticotropic hormone • Gonadotropin-releasing hormone • Growth hormone-releasing hormone • PTH • Leptin • Ca^{2+}

Table 22-3 (Continued)

Hormone Excess	Examples
Nuclear	• Androgen receptor • Estrogen receptor • Glucocorticoid receptor • Peroxisome proliferator activated receptor • Vitamin D receptor
Signaling pathway mutations	• Albright's hereditary osteodystrophy
Postreceptor	• Type 2 diabetes mellitus • Leptin resistance

* Of neuroendocrine origin, derived from primitive stem cells of the gut wall, but can occur throughout the body.

Table 22-4 Endocrine glands and autoimmune disease(s).

Clinical Syndrome	Organ	Prevalence (if known*)	Antibody	Antigen
Stimulating				
Graves' disease†	Thyroid	1 in 100	Thyroid-stimulating immune-globulin (TSI, TSAb)	Thyroid-stimulating hormone receptor
Neonatal thyrotoxicosis				
Destructive				
Autoimmune hypophysitis	Pituitary			
Selective hypopituitarism (e.g., growth hormone deficiency, diabetes insipidus)	specific cells			
Myxedema† (primary hypothyroidism)	Thyroid	1 in 100	Thyroid microsomal	Thyroid peroxidase enzyme (TPO)
			Thyroglobulin	Thyroglobulin
Primary hypoparathyroidism	Parathyroid		Parathyroid chief cell	
Addison's disease‡ (primary hypothyroidism)	Adrenal (adrenal cortex but sparing medulla)			
Type 1 diabetes mellitus	Pancreas beta-islet cells	1 in 500	Autoantibodies to GAD_{67} and GAD_{65}	Glutamic acid decarboxylase (GAD)
Pernicious anemia§ (stomach)	Gastric parietal cell intrinsic factor			
Primary ovarian failure	Ovary	1 in 500		
Primary testicular failure	Testis			
Vitiligo (skin)†	Skin melanocytes		Anti-melanocyte	

* Prevalence for Northern European/Caucasian populations.
Stomatognathic system manifestations:
† Associated with lichen planus, including oral lichen planus.
‡ Hyperpigmentation ("bronzing") and increased number of melanotic macules of the oral mucosa.
§Atrophic glossitis.
Associated diseases include myasthenia gravis and autoimmune liver diseases.

HYPOTHALAMUS AND PITUITARY

Hypothalamus

The hypothalamus (Figure 22-3) contains vital sensors to monitor and control key functions such as appetite, thirst, thermal regulation, the sleeping/waking cycle (circadian rhythm), the menstrual cycle, and the response to stress, exercise, and mood. It serves to integrate the many neural and endocrine inputs to control the release of pituitary hormone-releasing factors. The hypothalamic neurons secrete both pituitary hormone-releasing and pituitary-inhibitory factors (and hormones) via the portal (vein) system, which passes down the stalk into the pituitary.[19]

Pituitary Gland

The pituitary gland is a pea-sized structure situated at the base of the brain within the sella turcica, and is in intimate association with the hypothalamus. It plays a key role in the control of the endocrine system via feedback mechanisms, and hence has been termed the "conductor of the endocrine orchestra."[20]

The pituitary gland is divided into two anatomically, functionally, and developmentally distinct structures: the anterior and posterior lobes.

Anterior Pituitary (Adenohypophysis)

The anterior pituitary hormones (Figures 22-3 and 22-4) are under predominantly positive control by the hypothalamic-releasing hormones, apart from the release of prolactin, which is under tonic inhibition by dopamine. Therefore, pathologic conditions that interrupt the flow of hormones between the hypothalamus and the pituitary gland result in deficiencies of most hormones, but the oversecretion of prolactin. The anterior pituitary is a mixture of cells that produce GH, ACTH, TSH, LH, FSH, and prolactin. ACTH, TSH, FSH, and LH are all intermediaries in their respective endocrine axes; each responds to a specific hypothalamic hormone (Figure 22-5) and, in turn, acts upon an end-organ gland to bring about the endocrine response.

There are five major anterior pituitary axes:

- Gonadotrophin axis.
- Growth axis.
- Prolactin (lactation) axis.
- Thyroid axis.
- Adrenal axis.[21]

The role of the anterior pituitary hormone prolactin is for the initiation and maintenance of lactation. Prolactin levels are increased during pregnancy, breast-feeding, nipple stimulation, stress, and chest wall injury, and by medications with antidopaminergic properties (e.g., antipsychotics).

Posterior Pituitary (Neurohypophysis)

The posterior pituitary (Figures 22-3 and 22-4) is a group of neural cells that are an extension of the hypothalamus and have secretory capacity. The posterior pituitary only secretes two hormones, arginine vasopressin (AVP), also known as antidiuretic hormone (ADH), and oxytocin, both of which are nonapeptides (oligopeptides formed from nine amino acids; Figure 22-5). The primary physiologic functions of oxytocin include contraction of the myoepithelial cells of the alveoli of the mammary gland, which is important during lactation as part of the "let-down response," and contraction of the uterus during childbirth and immediately postpartum.

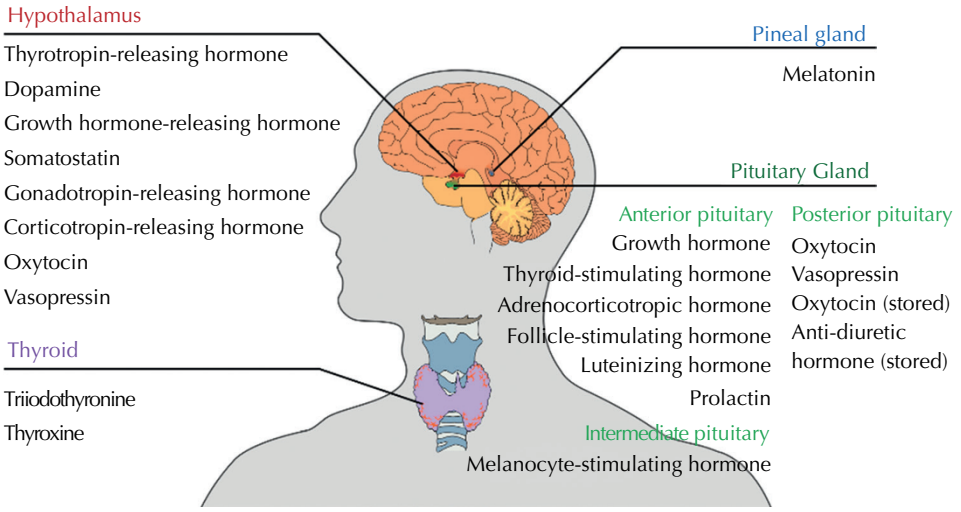


Figure 22-4 Endocrine system in the head and neck region. *Source:* https://commons.wikimedia.org/wiki/File:Endocrine_central_nervous_en.svg. Public domain..

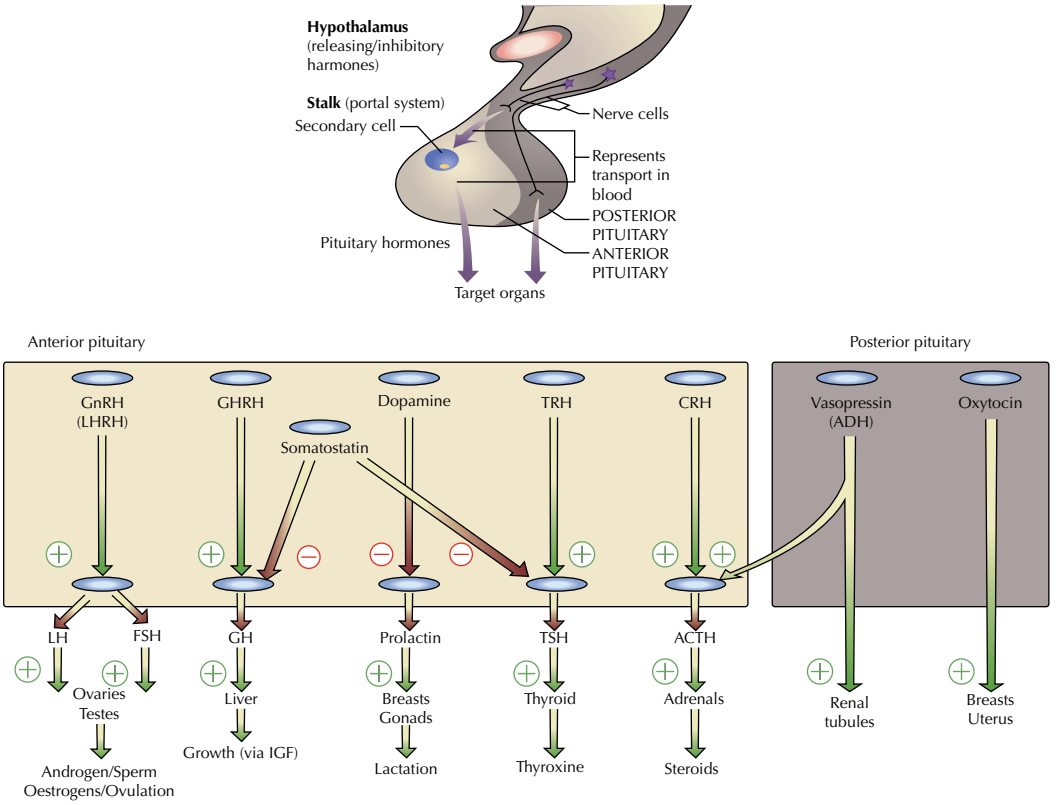


Figure 22-5 The hypothalamic-releasing hormones and their corresponding pituitary trophic hormones. ACTH, adrenocorticotrophic hormone; CRH, corticotrophin-releasing hormone; FSH, follicle-stimulating hormone; GH, growth hormone; GHRH, growth hormone-releasing hormone; GnHR, gonadotrophin-releasing hormone; LH, luteinizing hormone; LHRH, luteinizing hormone-releasing hormone; TRH, thyrotrophin-releasing hormone; TSH, thyroid-stimulating hormone. *Source:* Kumar PJ, Clark ML (Eds.). *Kumar and Clark's Clinical Medicine*, 9th edn. Edinburgh: Saunders; 2017. Reproduced with permission.

Hormone Excess

Hormone excess is seen with pituitary adenomas that are usually benign and slow growing. The symptoms related to the physical enlargement of the adenoma include visual impairment or headache. Occasionally these are detected incidentally as a finding on a magnetic resonance imaging (MRI) or computer tomography (CT) scan. They can result in increased secretion of the hormone(s) produced by the cells represented in these lesions and/or decreased secretion of other hormones due to compression by the tumor. In contrast, pituitary apoplexy (pituitary infarction) has a dramatic presentation with a sudden and severe headache, often with diplopia. Evaluation of masses within the sella turcica is best done with MRI (see Figure 22-6) and evaluation of the hormonal profile.

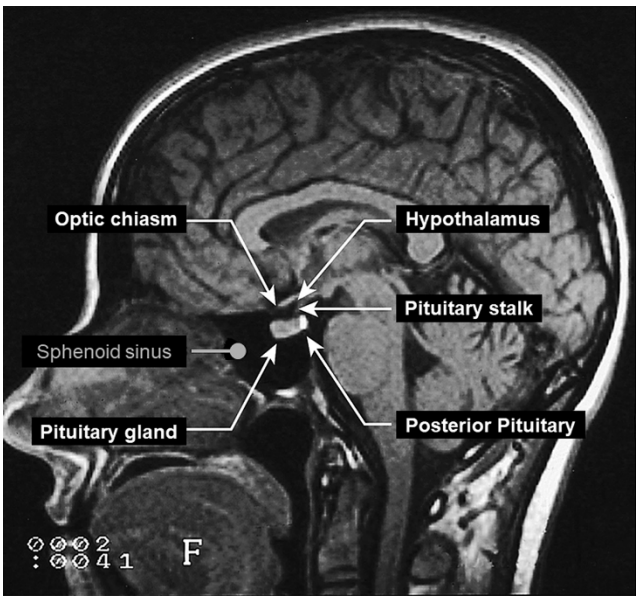


Figure 22-6 Magnetic resonance imaging (MRI) of a sagittal section of the brain, showing the pituitary fossa and adjacent structures. *Source:* Modified from Kumar PJ, Clark ML (Eds.). *Kumar and Clark's Clinical Medicine*, 9th edn. Edinburgh: Saunders; 2017. Reproduced with permission.

Hypopituitarism

Defects of the hypothalamic-releasing hormones or of the pituitary trophic hormones can be selective or multiple. Selective deficiencies of GH, LH/FSH, ACTH, TSH, and

vasopressin (ADH) are all seen from a variety of causes. Multiple deficiencies usually result from a tumor. There is generally a progressive loss of anterior pituitary function, with GH and the gonadotrophins usually being the first trophic hormones affected. Hyperprolactinemia, rather than prolactin deficiency, occurs relatively early, because of loss of tonic inhibitory control by dopamine. TSH and ACTH secretion is usually the last to be affected. Panhypopituitarism refers to deficiency of all anterior pituitary hormones and it is most commonly caused by pituitary tumors, or as a consequence of the surgery or radiotherapy used in the treatment of such tumors. ADH and oxytocin secretion will only be significantly affected if the hypothalamus is involved, either by a hypothalamic tumor or by suprasellar extension of a pituitary lesion. ADH and oxytocin deficiency is rarely seen with an uncomplicated pituitary adenoma. In general, the symptoms of deficiency of a pituitary-stimulating hormone are the same as primary deficiency of the peripheral endocrine end-organ; for example, TSH deficiency results in primary hypothyroidism and so causes similar symptoms due to lack of thyroid hormone secretion.[22]

Clinical Features

The symptoms and signs will reflect the extent of the hypothalamic and/or pituitary deficiencies, with mild deficiencies being generally clinically silent.

- *Secondary hypothyroidism* and *adrenal failure* both lead to tiredness and general malaise.
- *Hypothyroidism* results in weight gain, slowed mentation, slowness of action, dry skin, and cold intolerance.
- *Hypoadrenalism* causes mild hypotension, hyponatremia, and, ultimately, cardiovascular collapse during severe intercurrent stressful illness.
- *Gonadotrophin/gonadal deficiency* leads to loss of libido, loss of secondary sexual hair, amenorrhea, and erectile dysfunction.
- *Hyperprolactinemia* can cause galactorrhea and hypogonadism, including amenorrhea.
- *GH deficiency* causes growth failure in children and impaired wellbeing in some adults.
- *Weight increase* can be due to hypothyroidism.
- *Weight loss* can occur with severe combined deficiency (pituitary cachexia).
- *Panhypopituitarism* when long-standing gives the classic picture of pallor with hairlessness ("alabaster skin").

Treatment entails hormone replacement by synthetic equivalents. Steroid and thyroid hormones are essential for life. Both are given as oral replacement drugs, as in primary thyroid and adrenal deficiency, aiming to restore biochemical normality (see Table 22-5).

Table 22-5 Hypopituitarism: hormone replacement regimens.

Axis	Replacement Regimen
Adrenal	• Hydrocortisone 15–40 mg daily (starting dose 10 mg on rising/5 mg lunchtime/5 mg evening) Normally no need for mineralocorticoid replacement
Thyroid	• Levothyroxine 100–150 μg daily
Gonadal	
Male	• Testosterone—intramuscular, oral, transdermal, or implant
Female	• Estrogen/progesterone (cyclical)—orally or as patch
Fertility	• Human chorionic gonadotrophin *plus* Follicle-stimulating hormone (purified or recombinant) or gonadotropin-releasing hormone—for testicular development, spermatogenesis, or ovulation
Growth	• Children—recombinant growth hormone (GH); used to achieve normal growth in children • Adults—advocated for replacement therapy; GH has effects on muscle mass and wellbeing
Thirst	• Desmopressin 10–20 μg, 1–3 times daily by nasal spray or orally 100–200 μg 3 times daily • Carbamazepine, thiazides, and chlorpropamide—very occasionally used in mild diabetes insipidus
Lactation (breast)	• Dopamine agonist (e.g., cabergoline 500 μg weekly)

Source: Fleseriu M, Hashim IA, Karavitaki N, et al. Hormonal replacement in hypopituitarism in adults: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2016;101(11):3888–3921.

ABNORMALITIES OF GROWTH AND STATURE

Growth Hormone

GH is the pituitary factor responsible for growth in humans. GH secretion is stimulated by growth hormone-releasing hormone (GHRH), released into the portal system from the hypothalamus (Figure 22-7). There is a separate GH-stimulating system that interacts with ghrelin, a hormone that is synthesized by the stomach. It is unknown how the two systems interact. GH binds to receptors mainly found on liver cells, which results in turn in the release of IGF-1, for which there are multiple binding proteins (IGF-BP) in the plasma. Of these, IGF-BP3 can be measured to assess GH status. The metabolic actions of this system are increased collagen and protein synthesis; retention of

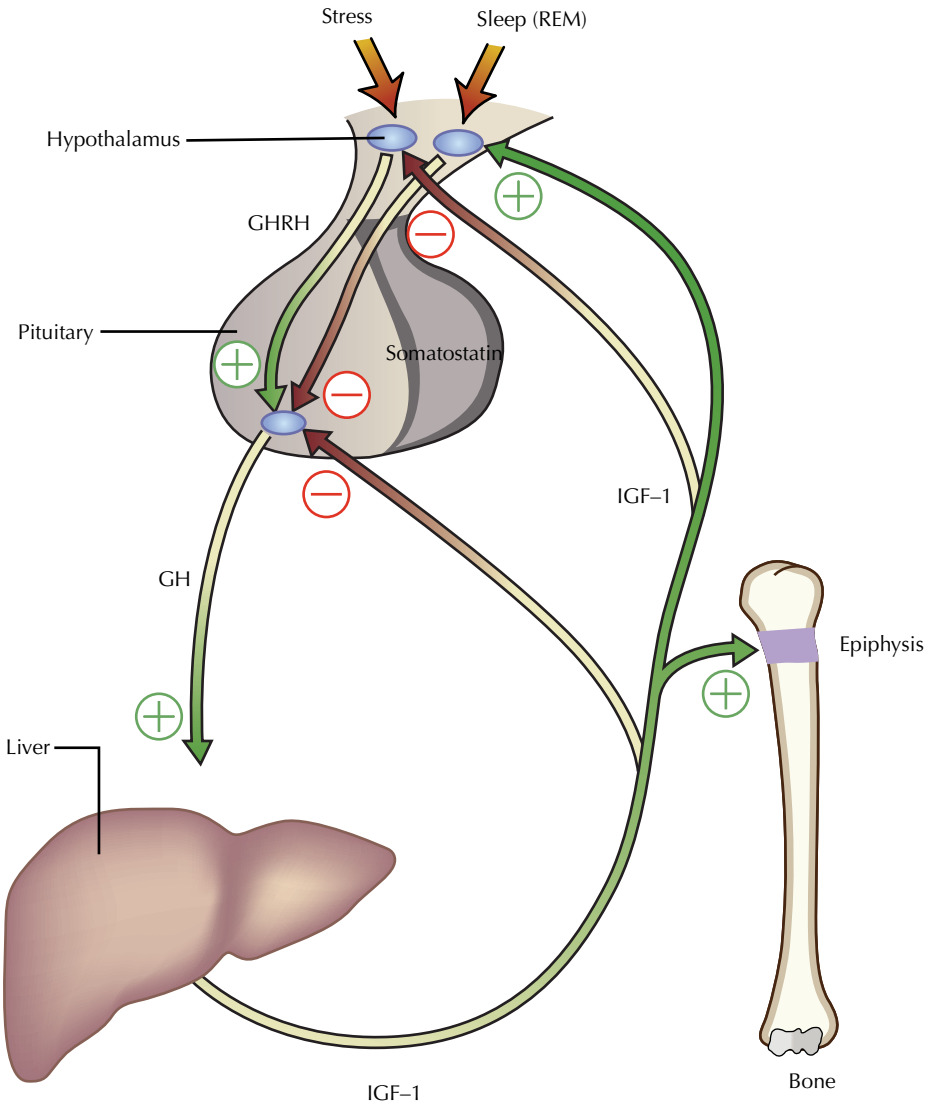


Figure 22-7 Growth hormone (GH): release and action. Pituitary GH is secreted under dual control of growth hormone-releasing hormone (GHRH) and somatostatin, and stimulates release of insulin-like growth factor 1 (IGF-1) in the liver and elsewhere. IGF-1 has peripheral actions, including bone growth by acting on the epiphyseal plate (epiphysis). *Source:* Kumar PJ, Clark ML (Eds.). *Kumar and Clark's Clinical Medicine*, 9th edn. Edinburgh: Saunders; 2017. Reproduced with permission.

calcium, phosphorus, and nitrogen (necessary for anabolism; i.e., the building of molecules); and opposing the actions of insulin. GH release is intermittent, mainly nocturnal during REM sleep, and is significantly increased during adolescence, but afterward declines.

Apart from GH, the following factors play a role in the normal linear growth of humans:

- *Genetics*: children of short parents will probably be short and vice versa.
- *Nutrition*: inadequate nutrients result in impaired growth, either from inadequate dietary intake or small bowel disease, for example coeliac disease.
- *General health*: serious systemic disease, such as chronic infection, will impair growth.
- *Intrauterine growth retardation*: this will result in poor long-term growth, whereas premature infants tend to catch up.
- *Emotional deprivation and psychologic factors*: these play a role in growth and development, although the mechanisms are complex and not fully understood.

Growth Assessment and Treatment

Growth charts and associated computer programs are now available for national and specific ethnic groups to monitor

and predict a child's final height. The Centers for Disease Control and Prevention (CDC) have readily available (downloadable) growth charts consisting of a series of percentile curves that illustrate the distribution of selected body measurements in US children (Figures 22-8 and 22-9).[23,24] These growth charts are also essential for predicting the treatment and prognosis of orthodontic and/or orthognathic treatment.[25]

Growth Failure (Short Stature)

This is usually noted by the child's parents. Height velocity is more helpful than current height. This requires at least two measurements some months apart and, ideally, multiple serial measurements. Height velocity is the rate of current growth (centimeters per year), while the current attained height is largely dependent upon previous growth. Computer programs are available to calculate the key indices, which include standard deviation scores based on the degree of deviation from age/sex norms.[26]

Further investigations include dynamic assessment of GH levels, IGF and IGF-BP3 blood levels, thyroid function tests, and assessment of bone age, by radiographs of the nondominant wrist and karyotyping in females for Turner's syndrome.[27]

Risk Factors for Short Stature

Risk factors for short stature include:[28]

- Intrauterine growth retardation, and weight and gestation at birth.
- Systemic disorders, especially small bowel disease.
- Congenital abnormalities (i.e., skeletal, chromosomal, or other).
- Endocrine status, particularly thyroid.
- Dietary intake.
- Drugs, especially steroids for asthma.
- Emotional, psychological, family, and school problems.

A child with normal growth velocity is unlikely to have significant endocrine disease and the most common cause of short stature in this situation is pubertal or "constitutional" delay. However, low growth velocity without an apparent systemic cause requires investigation (Table 22-6), as does sudden cessation of growth, since this suggests major physical disease, and in the absence of findings of systemic disease then a cerebral tumor or hypothyroidism is most likely.

Tall Stature

Tall stature (as opposed to gigantism/acromegaly) is most commonly hereditary, because of having tall parents. However, if the child's stature is usually tall and not consistent with the stature of the parents, chromosomal abnormalities such as Klinefelter syndrome or Marfan syndrome, or metabolic abnormalities, need to be considered. GH excess is a very rare cause and is usually clinically evident.

Acromegaly and Gigantism (Growth Hormone Excess)

GH is released from the somatotropic cells within the lateral wings of the anterior pituitary gland and is the primary trophic hormone responsible for postnatal growth and development. GH excess causes what is more formally termed *pituitary gigantism* in children if this occurs before fusion of the epiphyseal plate (growth). Gigantism is a nonspecific term that denotes excessive growth in a pediatric patient.[29] GH excess results in *acromegaly* if it occurs after the bony growth plates have fused. In almost all cases this is due to GH-secreting pituitary adenoma.

GH's major trophic effect is the release of IGFs from the liver. IGFs, as their name suggest, are proteins with significant homology to insulin, with a wide range of functions, but principally act to increase bone growth (specifically bone length). Although many cells have GH receptors and may respond to GH, the vast majority of the growth-stimulating effects of GH are mediated by IGF-1. GH release is under positive regulation by the hypothalamic peptide GH-releasing hormone. The amount and pattern of GH production and IGF release change markedly across the life cycle, with maximal release during the intense growth periods of late childhood and adolescence and low levels with advanced age. GH is released from the pituitary in a pulsatile fashion, with peak secretion at night. Thus, serum GH values vary considerable over the course of a 24-hour period, so a random sample may not reliably indicate true GH levels. In contrast, IGF-1 serum levels are relatively constant over the course of the day, so an IGF-1 sample can be taken at any time of the day and is indicative of GH levels.

Gigantism is very rare, with 0.6% reported in a large pediatric cohort.[30] Acromegaly is rare, with an overall prevalence of estimated prevalence in Europe of 30–70 individuals per million, affecting men and women equally.[31] The rapid growth seen with gigantism can be distinguished from that of precocious puberty. In gigantism, growth occurs in the absence of early secondary sexual characteristics, as the pituitary tumors (somatotroph adenomas) that lead to GH excess result in the loss of production of other pituitary hormones, particularly the gonadal trophic hormones, FSH, and LH, which are responsible for sexual development. Mild to moderate obesity is also commonly seen in these patients.

The mean age at diagnosis of acromegaly is usually 40–45 years, but as the progression of disease is so slow, the interval from the onset of symptoms until diagnosis can be as much as 12 years. Manifestations include the classic facial appearance of coarse facies, macrognathia, macroglossia,

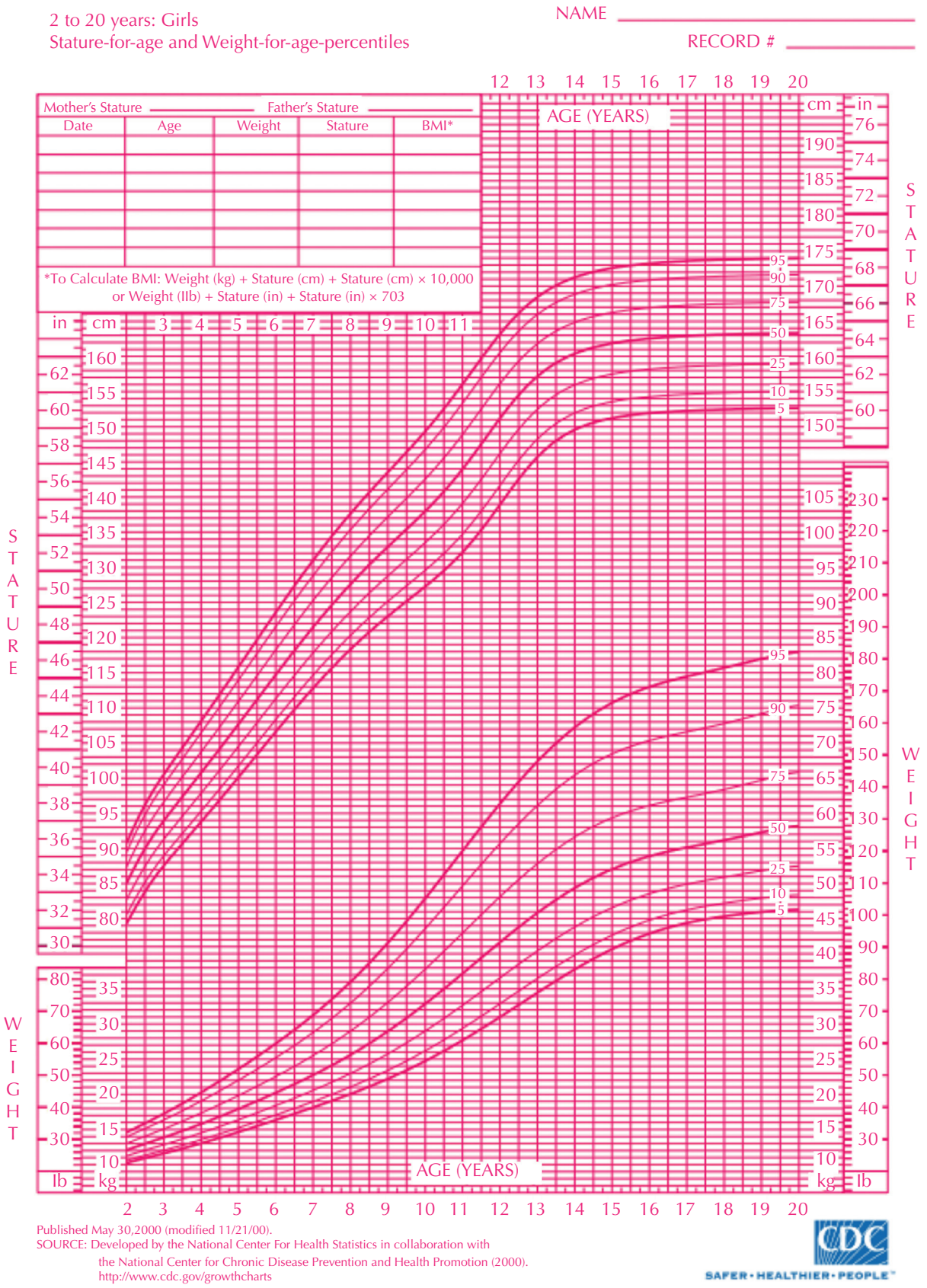


Figure 22-8 Height chart for girls.

2 to 20 years: Boys
Stature-for-age and Weight-for-age-percentiles

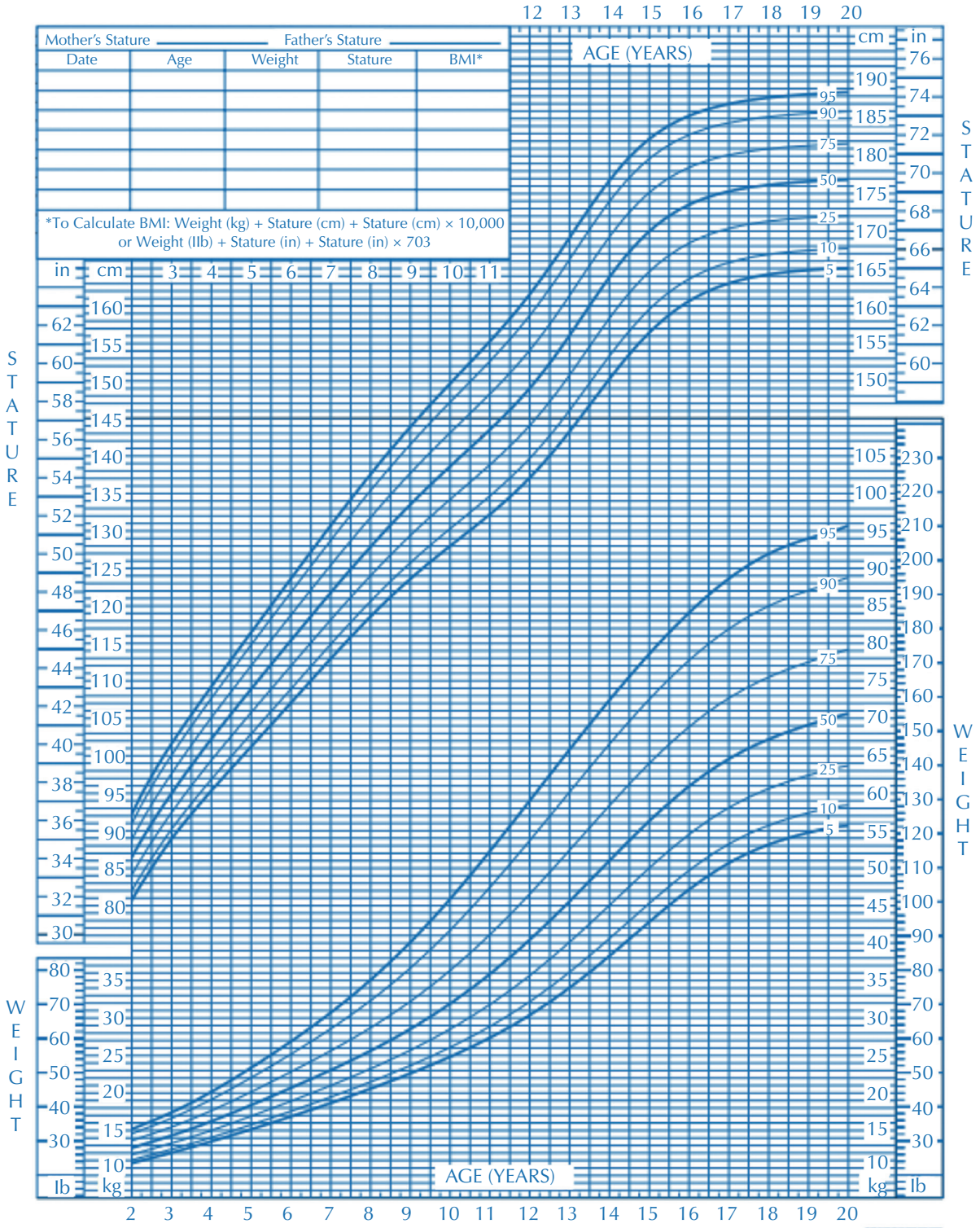
NAME _____

RECORD # _____

Mother's Stature _____ Father's Stature _____

Date	Age	Weight	Stature	BMI*

*To Calculate BMI: Weight (kg) + Stature (cm) + Stature (cm) × 10,000
or Weight (lb) + Stature (in) + Stature (in) × 703



Published May 30,2000 (modified 11/21/00).
SOURCE: Developed by the National Center For Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).
http://www.cdc.gov/growthcharts

CDC
SAFER • HEALTHIER • PEOPLE™

Figure 22-9 Height chart for boys.

Table 22-6 Clinical features of common causes of short stature.

Cause	Family History	Growth Pattern	Bone Age	Comments
Constitutional delay	Positive	• From birth: slow • Growth: delayed • Puberty: late but spontaneous	Moderate delay	• Difficult to differentiate from GH deficiency • Growth velocity assessment essential
Familial short stature	Positive	• From birth: slow • Growth: normal • Puberty: normal onset and growth	Normal	• Check height of parents/family members • Growth velocity: normal
Growth hormone (GH) deficiency	Rare	• From birth: slow • Overweight • Puberty: delayed	Moderate delay Worsens over time	• Need high level of clinical suspicion • Investigate early
Primary hypothyroidism	Rare	• From birth: slow • Puberty: delayed	Marked delay	• Check thyroid-stimulating hormone and T4
Small bowel disease • Celiac disease • Crohn's disease • Ulcerative colitis	Possibly	• From birth: slow • Growth: slow • Thin for height • Puberty: delayed	Delayed	• Check for irregular bowel habit, colic • Oral manifestations of celiac disease/ inflammatory bowel disease (IBD) • Check for anemia • Serology: celiac and IBD

large diastemas, and enlargement of the nose and frontal bones (frontal bossing) (Figure 22-10). Soft tissue edema, due to a direct effect of GH on sodium retention, leads to a "doughy" feel to the hands and feet, as well as an increase in shoe, hat, glove, and ring sizes. Patients can also have increased sweating, deepening of the voice due to enlargement of the thyroid cartilage and vocal cords, enlargement of the synovium and cartilages with hypertrophic arthropathy (knees, ankles, hips, spine, and other joints), skin tags, nerve compression (causing paresthesia of the hands, as in carpal tunnel syndrome), enlargement of the soft tissues of the pharynx and larynx (which can lead to obstructive sleep apnea), increased risk of uterine leiomyomata, colonic polyps, and organomegaly (including the thyroid, heart, liver, kidneys, and prostate). Some 50% of patients with GH excess develop hypertension, 10% develop cardiomegaly with heart failure, which accounts for much of the increased mortality associated with acromegaly and 30% develop insulin resistance or T2DM. Surprisingly, patients seldom independently seek care as the changes are so insidious, and treatment is often initiated when a relative or friend, who has not seen the patient for some time, notes the typical changes as described here.[17]

Diagnosis

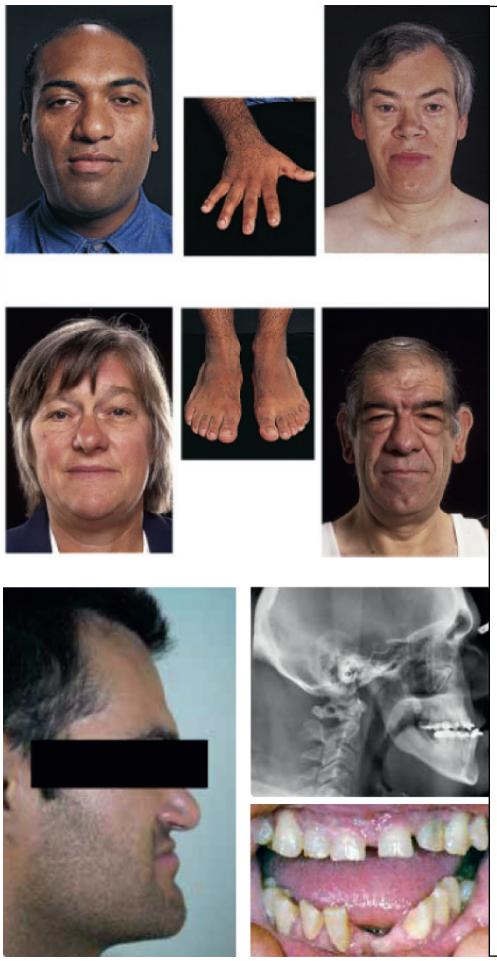
Diagnosis is often made on the clinical presentation, with a third diagnosed by the changes in appearance, a quarter because of the visual field defects and/or headache, and the reminder by an astute clinician, including the patient's family physician (investigating potential causes for hypertension), dermatologist, and in particular the dentist.[32] Key investigations are serum GH levels, IGF-1 levels, MRI, which will reveal a pituitary adenoma, visual field examination, and glucose challenge test.

Treatment

Untreated acromegaly results in significant morbidity and increased rate of premature death. The aims of treatment are to establish a "safe" GH level and a normal IGF-1 level. If present, hypopituitarism also needs to be addressed. Concurrent hypertension and/or diabetes should be treated with conventional agents, but usually resolve with treatment of the acromegaly.

Treatment is usually surgical, most commonly by a transsphenoidal approach, or transfrontal for large adenomas, with radiotherapy reserved for situations in which GH levels fail to normalize. There are three potential targets for medical therapy: (1) somatostatin receptor agonists, either octreotide or lanreotide, which are given as monthly depot injections—these are generally effective, but do increase the risk for the development of gallstones; (2) dopamine agonists, either bromocriptine or cabergoline, which are best for patients with mild residual disease; and (3) growth hormone receptor antagonist, that is pegvisomant, a genetically modified analogue of GH that is reserved for patients who otherwise fail all other interventions.[33]

Symptoms
- Hypertension
- Dyslipidemia
- Obstructive sleep apnea (OSA)
- Headaches
- Deepening voice
- Visual changes (bitemporal hemianopsia)
- Gastroesophageal reflux disease (GERD)
- Colon polyps
- Insulin resistance
- Renal failure
- Osteopenia
- Arthritis
- Carpal tunnel syndrome
- Hypogonadism
- Amenorrhoea
- Erectile dysfunction



Signs
- Cardiomegaly
- Heart Failure
- Valvopathy
- Visual deterioration
- Deepening voice
- Diabetes mellitus
- Hyperhidrosis (excessive perspiration
- Changed appearance
- Enlarged hand and feet

Stomatognathic
- Prognathism
- Macroglossia
- Frontal bossing
- Class III malocclusion
- Anterior open bite
- Increasing interdental spacing and diastemas
- Thickened lips

Figure 22-10 Symptoms and signs of acromegaly. *Sources:* Kumar PJ, Clark ML (Eds.). *Kumar and Clark's Clinical Medicine*, 9th edn. Edinburgh: Saunders; 2017. Prognathic jaw clinical photo and radiograph from Ivry G, Felsenfeld AL. Acromegaly: a dental disease? *J Calif Dent Assoc*. 2016;44(9):577–580. Reproduced with permission.

Stomatognathic Manifestations and Complications of Acromegaly

The predominant clinical findings in acromegaly—prognathism with evolving or established class III malocclusion; the development of significant diastemas, especially of the mandibular dentition; and radiographic findings of enlarged sella and frontal bossing (on lateral cephalogram)—mean that hygienists, dentists, and dental-related specialists are key in making the initial diagnosis of acromegaly. Following diagnosis and appropriate treatment, oral health professionals can facilitate oral rehabilitation. However, even patients with treated acromegaly can still have ongoing disease-related morbidities, which need to be identified on taking a comprehensive medical history. The key concerns in particular are treatment-refractory hypertension, valvopathy, and obstructive sleep apnea (OSA). The sleep apnea seen in association with acromegaly is predominantly obstructive and is related to thickening of walls of the upper airway, including the soft palate. However, the patient with acromegaly and sleep apnea presents special problems, as retropositioning the mandible to treat the prognathism is inconsistent with the principles involved in the management of OSA, necessitating alteration in conventional treatment planning.[34,35]

HYPERPROLACTINEMIA

Hyperprolactinemia can be caused by hyperplasia of the so-called lactotroph cells (prolactinomas) or decreased tonic dopaminergic inhibition of prolactin secretion (e.g., compression by a central nervous system tumor).[36] Prolactinomas can cause hypogonadism by suppressing gonadotropin secretion. In women, hypogonadism results in low serum estrogen levels that can present as oligomenorrhea, amenorrhea, infertility, and osteoporosis. In men, hypogonadism causes low serum testosterone concentrations that result in decreased libido and energy, decreased facial hair growth, loss of muscle mass, and osteoporosis. Hyperprolactinemia in men may also

be associated with impotence even when the serum testosterone concentration is normal. It can cause galactorrhea (leakage of milk from the breast other than during lactation) in women, but this only occurs very rarely in men.

Prolactinomas are relatively common, accounting for 30–40% of all clinically recognized pituitary adenomas. The diagnosis is made more frequently in women than in men, especially between the ages of 20 and 40 years, presumably because the hyperprolactinemia disrupts their menstrual cycle.[37] Such tumors can be identified by the enlargement of sella turcica incidentally observed on lateral cephalograms.[38]

Prolactinomas can be treated with dopamine agonists, such as cabergoline or bromocriptine. These drugs have the dual effect of decreasing hormone secretion and tumor size. If the adenoma does not respond to increasing doses of these medications or there is imminent visual loss, transsphenoidal surgery is required for removal of the tumor.[39]

DISORDERS OF ANTIDIURETIC HORMONE

Thirst Axis

Thirst and the symptoms of thirst, xerostomia and the signs of dehydration, namely hyposalivation and dry mucous membranes of the mouth, are of course of great relevance to the clinical practice of oral healthcare providers. Thirst and water regulation are largely controlled by vasopressin, also known as antidiuretic hormone (ADH). ADH is synthesized in the hypothalamus and then migrates in neurosecretory granules via axonal pathways to the posterior pituitary. Pituitary diseases that spare the hypothalamus do not lead to ADH deficiency, as the hormone still can "leak," even from the end of a damaged axon.

The kidney is the predominant site of action of ADH at normal concentrations. ADH stimulation of the vasopressin-2 (V2) receptors allows the collecting ducts to become permeable to water, via the migration of aquaporin-2 water channels, resulting in the reabsorption of hypotonic luminal fluid. ADH acts to reduce diuresis (i.e., less urine) and results in retention of water. At high concentrations, ADH can also cause vasoconstriction, via the V1 receptors present in the vascular tissues, thus limiting blood supply to the kidneys, resulting in further water retention and less urine output.

ADH is regulated by osmoreceptors in the anterior hypothalamus that can sense plasma osmolality. ADH secretion is suppressed at levels below 280 mOsm/kg, thus allowing maximal urine formation (diuresis). Above this level, plasma vasopressin increases in direct proportion to plasma osmolality. At the upper limit of normal (295 mOsm/kg), maximum antidiuresis is achieved (little if any urine production), with thirst being experienced at about 298 mOsm/kg.

DIABETES INSIPIDUS

Disorders of ADH are in essence disorders of water balance. ADH deficiency is termed diabetes insipidus (DI) and is a syndrome characterized by the inability for the kidneys to retain water.[40] It can be caused by inadequate pituitary production of ADH (termed *central DI*), or resistance to the actions of ADH on the kidneys (termed *nephrogenic DI*). DI can also be gestational, or present as an iatrogenic artefact of alcohol or some types of drug abuse. The primary presenting symptom is polyuria (>3 L/d), and resultant hypernatremia, nocturia, and compensatory polydipsia (excessive thirst/water intake). Daily urine output may reach as much as 10–15 L, leading to dehydration that may be very severe if the thirst mechanism or consciousness is impaired or if the patient is denied fluid. Diagnosis of DI is made by a water deprivation test, requiring medical supervision.[41]

Treatment is with the synthetic vasopressin (ADH) analogue desmopressin (also known as DDAVP, 1-desamino-8-d-arginine vasopressin, desamino cys-1-d-arginine-8 vasopressin), which has the advantages of a longer duration of action than vasopressin and no vasoconstrictive effects. It is reliably given by an intranasal spray 10–40 μg once or twice daily, but can also be given orally (100–200 μg three times daily or intramuscularly 2–4 μg daily). For patients with DI, a reversible underlying cause (e.g., a hypothalamic tumor) should be investigated for and treated, if found. Other causes of polyuria and polydipsia include diabetes mellitus (DM), hypokalemia, and hypercalcemia, which should be excluded. In the case of DM, the cause is an osmotic diuresis secondary to glycosuria, which leads to dehydration and increased thirst, owing to the hypertonicity of the extracellular fluid.[42]

SYNDROME OF INAPPROPRIATE ANTIDIURETIC HORMONE

Excessive ADH (syndrome of inappropriate antidiuretic hormone, SIADH) is a syndrome of too much total body water and consequent hyponatremia, of which the electrolyte disturbance is the main concern and the cause of the presenting clinical features.[43] Major causes of SIADH include central nervous system (CNS) disturbances such as stroke, infection, trauma, and hemorrhage. Other causes are medications, serious illness (especially in the elderly), and some types of cancer. The clinical presentation tends to be slow, with the patient exhibiting confusion, nausea, irritability, and, later, fits and coma, but with no edema. Mild symptoms usually occur with plasma sodium levels below 125 mmol/L and serious manifestations occurring below 115 mmol/L.[44] The elderly may show symptoms with milder abnormalities. SIADH needs to be differentiated from dilutional hyponatremia

Table 22-7 Physiologic effects of the thyroid hormones.

Target Organs/Tissues	
Cardiovascular system	↑ Heart rate ↑ Cardiac output
Respiratory center	Maintains normal • Hypoxic drive • Hypercapnic drive (response to CO_2 concentration in the blood)
Neuromuscular function	↑ Muscle contraction and relaxation ↑ Muscle protein turnover
Sympathetic nervous system	↑ Catecholamine sensitivity ↑ β-adrenergic receptor numbers on: heart, skeletal muscle, adipose cells, and lymphocytes ↓ Cardiac α-adrenergic receptors
Gastrointestinal system	↑ Gut motility
Metabolism Carbohydrate	↑ Hepatic gluconeogenesis/glycolysis ↑ Intestinal glucose absorption
Lipid	↑ Lipolysis ↑ Cholesterol synthesis and degradation
Bone	• Bone turnover and resorption
Hematologic system	• Oxygen release by red blood cells to tissues

due to excess infusion of glucose/water solutions or diuretic administration (thiazides or amiloride). ACTH deficiency can give a very similar biochemical picture to SIADH; therefore, it is necessary to ensure that the HPA axis is intact, particularly in neurosurgical patients, in whom consequently ACTH deficiency is relatively common.

Management entails identifying the underlying cause and correcting this, when possible. Symptomatic relief includes fluid restriction, with an intake of only 500–1000 mL water daily; if complied with, this will usually correct the biochemical abnormalities. Such fluid restriction can result in salivary hypofunction and so directly contribute to higher rates of dental decay, and candidiasis.[45,46] Newly available, ADH (V2) antagonists (e.g., tolvaptan, sold as Samsca® in the United States; Otsuka America Pharmaceutical, Rockville, MD, USA) are being used with good effect.[47]

THYROID DISEASE

Thyroid disease occurs frequently and is the most common endocrine disease. The thyroid gland synthesizes three hormones: (1) thyroxine (T4), which is a prohormone; (2) triiodothyronine (T3), the active hormone that is critical in regulating the body's metabolic rate; and (3) calcitonin, which regulates bone metabolism. Adequate levels of thyroid hormone are essential in infants for normal CNS development, in children for normal skeletal growth and maturation, and in adults for the normal function of multiple organ systems (Table 22-7). In general, there are five main types of thyroid disease, and disease can be intercurrent in the same patient:

- Hypothyroidism (termed "myxedema" when it occurs in adults and "cretinism" when it occurs in infants and children), caused by a deficiency of thyroid hormones.
- Hyperthyroidism (thyrotoxicosis), due to an excess of thyroid hormones with consequent significant clinical issues, especially of the cardiovascular system.
- Abnormal thyroid function tests (TFTs), in an otherwise euthyroid (the state of having normal thyroid gland function) patient.
- Structural abnormalities, mainly goiter, which may be seen as diffuse enlargement of the thyroid gland, or single or multiple nodules, due to focal enlargement of only a portion of the gland,
- Neoplasms.

Epidemiology

Thyroid disease has prevalence of 6% as of 2019 and it is estimated that over 12% of Americans will develop some form of thyroid disease over the course of their lifetime.[48] Of these, some 60% are unaware of their condition. Thyroid diseases

are far more common in women. The management for most thyroid disorders is life-long and well tolerated. In the United States, autoimmune inflammation is the most common cause of thyroid disease whilst worldwide hypothyroidism and goiter due to iodine deficiency is much more common.[49] Although thyroid nodules are common, thyroid cancer is rare. Thyroid cancer accounts for less than 1% of all cancer in the US,[50] although it is the most common endocrine tumor and makes up greater than 90% of all cancers of the endocrine glands.[51]

Thyroid Gland: Anatomy and Physiology

The thyroid gland consists of two lateral lobes connected by an isthmus, closely attached to the thyroid cartilage and to the upper end of the trachea, and thus moves on swallowing. Embryologically, it originates from the base of the tongue and descends to the middle of the neck. Remnants of thyroid tissue can sometimes be found at the base of the tongue (lingual thyroid) and along the line of its descent.

Internally, the thyroid gland consists of follicles lined by cuboidal epithelioid cells within which is colloid (iodinated glycoprotein thyroglobulin), synthesized by the follicular cells. Each follicle is surrounded by basement membrane, and between them are parafollicular cells containing the C cells that secrete calcitonin. The thyroid also synthesizes triiodothyronine (T3), which acts at the cellular level, and L-thyroxine (T4), which is the prohormone. Inorganic iodine is essential for the synthesis of the two thyroid hormones and the precursor molecule, thyroglobulin (Figure 22-11). Globally, dietary iodine deficiency is a major cause of thyroid disease. Dietary supplementation of salt and bread has reduced the number of areas where "endemic goiter" still occurs. Surprisingly, in Western countries iodine deficiency is now a concern, given the decline in adventitious iodine in dairy products with use of noniodoform disinfectants in milk production and "food fads," with the use of noniodized rock salt in place of iodized salt in cooking. In the United States iodine intakes have fallen, and it is uncertain whether the iodine status for most pregnant woman is satisfactory, leading to calls for systematic iodine supplementation.[52]

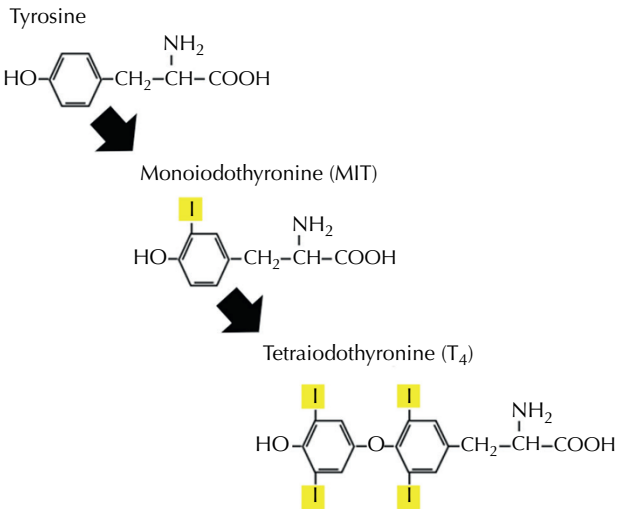


Figure 22-11 The conversion of the amino acid tyrosine, with the addition of iodine (yellow) atoms.

In plasma, more than 99% of all T4 and T3 is bound to hormone-binding proteins: TBG, thyroid-binding prealbumin, and albumin. Only unbound—that is, free—hormone is biologically active. Circulating T4 is peripherally deiodinated to T3, which has a far greater affinity for its receptors than T4. T3 binds to the two thyroid hormone nuclear receptors (TR-α and TR-β) of the target cells to cause gene transcription.

Control of the hypothalamic-pituitary-thyroid axis is, as is universal throughout the endocrine system, by negative feedback control. Thyrotropin-releasing hormone (TRH) is a peptide produced in the hypothalamus, which stimulates the pituitary to secrete TSH (Table 22-8). TSH, in turn, stimulates growth and activity of the thyroid follicular cells, which consequently secrete T3 and T4 into the circulation. T3 and T4 both exert negative feedback on the hypothalamus, leading to a decrease in the secretion of TRH and so a decrease in TSH and in turn a decrease in T3 and T4. The decrease in circulating T3 and T4 prompts increased release of TRH and, again, in turn an increase in TSH and then T3 and T4.

Hypothyroidism

Hypothyroidism, defined as the inadequate release of the two thyroid hormones T3 and T4, is usually primary; that is, due to disease of the thyroid gland, However, it may be secondary, due to disease of hypothalamic or pituitary, with consequent reduction in TSH, and so a decline in T3 and T4 release by an otherwise intact thyroid gland.

Hypothyroidism is one of the most common endocrine conditions, with a prevalence rate of 4.6% for the US population. Approximately 0.3% present with clinically overt disease and the remaining 4.3% with subclinical disease (decreased T3 and T4 levels but no clinical evidence of disease).[53] Of those with subclinical hypothyroidism, 2% per annum develop clinically evident hypothyroidism, hence the lifetime prevalence for an individual is higher—perhaps as high as 9% for women and 1% for men, with mean age at diagnosis around 60 years.[54]

Causes

Autoimmune

- *Atrophic (autoimmune) thyroiditis.* This is associated with the development of antithyroid autoantibodies with

Table 22-8 Thyroid function tests and role in clinical practice.

Normal Hypothalamic-Pituitary Function

Indication	Serum TSH*	Serum T4	Serum T3
Euthyroid	Normal	Normal	Normal
Primary hypothyroidism	High	Low	Normal or low
Subclinical hypothyroidism	High	Normal	Normal
Hyperthyroidism	Low	High or normal	High
Subclinical hyperthyroidism	Low	Normal	Normal

- If serum TSH is normal—no further testing indicated or required.
- If serum **TSH is HIGH**—the lab will add free T4 to determine degree of ***hypo***thyroidism.
- If serum TSH is LOW—both free T4 and T3 are added to the patient's sample to determine degree of ***hyper***thyroidism.

Clinical indications for additional testing:

- **Pituitary/hypothalamic disease suspected,** e.g., a young woman with amenorrhea and fatigue: test TSH.
- **Patient has symptoms of hyper- or hypothyroidism and normal TSH result:** test T4.

* With central hypothyroidism, serum TSH may be low, normal, or slightly high.
T3, triiodothyronine; T4, thyroxine; TSH, thyroid-stimulating hormone.

consequent lymphoid infiltration of the thyroid glands, and eventual atrophy and fibrosis. It is associated with other autoimmune conditions including pernicious anemia, vitiligo, and other endocrinopathies.[55,56]

- *Hashimoto's thyroiditis.* This is most common in middle-aged women. High levels of autoantibodies are developed and directed against thyroid peroxidase (the enzyme that coverts T4 to T3).Atrophic changes are followed by regeneration, with this cycle leading to clinically evident generalized goiter, which is firm and hard on palpation.
- *Postpartum thyroiditis.* A destructive form of thyroiditis associated with the immune changes of pregnancy, this can occur up to year post parturition. It confers, as seen with most pregnancy-associated endocrine disease, a lifetime risk for the development of permanent hypothyroidism, necessitating ongoing screening for affected women.[57]

Defective Hormone Synthesis

- *Iodine deficiency*. This can result in endemic goiter, which can be massive, due to borderline iodine deficiency with consequent TSH stimulation, and therefore hyperplasia and hypertrophy of the thyroid gland. At a global scale, approximately 2 billion people suffer from iodine deficiency, of which approximately 50 million people present clinical features of hypothyroidism. The effect of chronic iodine deficiency and related hypothyroidism leads to cretinism in children, which causes growth delay, short stature, and severe cognitive impairment.[58]

Clinical Features

Hypothyroidism produces many symptoms and signs, but these can be subtle and difficult to distinguish from other causes of tiredness and fatigue. The alternate term "myxedema" refers to the typical appearance of patients with long-standing significant hypothyroidism, due to the accumulation of mucopolysaccharides in the subcutaneous tissues, presenting with mucinous, nonpitting edema, particularly of the hands, feet, and eyelids. The clinical presentation includes dry hair, thick skin, deepening of the voice, weight gain, complaints of cold intolerance, and bradycardia. Diagnosis is difficult in children, young women, and the elderly and TSH and serum T3 and T4 should be undertaken to exclude hypothyroidism in these subjects, even if only suspected. If hypothyroidism is proven (low T3 and T4), investigations are required to differentiate primary disease from diseases affecting the hypothalamus-pituitary-thyroid axis.[59]

Treatment

The commonest treatment for hypothyroidism is synthetic T4 (thyroxine), levothyroxine (sold in the United States as Synthroid®, AbbVie, North Chicago, IL, USA; Levoxyl®, Pfizer Medical, New York, USA; Tirosint®, IBSA Pharma, Parsippany, NJ, USA; and Euthyrox®, Provell Pharmaceuticals, Honey Brook, PA, USA).[60] The goals of treatment are amelioration of the patient's symptoms, normalization of the serum TSH levels, reduction in the size of goiter (if present), and, of most concern, avoidance of overtreatment (iatrogenic thyrotoxicosis). Both the initial and maintenance doses of levothyroxine are titrated

to effect, based on the serum T4 and TSH and serial electrocardiograms, to exclude the development of atrial fibrillation, a known complication of hyperthyroidism.[61] The starting dose is 100 μg/daily for the young and fit with no cardiovascular disease; 50 μg/daily for the small, frail, and elderly; and even lower (i.e., 25 μg/daily) in patients with severe, long-standing hypothyroidism or with a history of ischemic heart disease. The usual maintenance dose is 100–150 μg daily.

Myxedema Coma and "Madness"

This can occur as the culmination of severe, long-standing hypothyroidism or can be precipitated by an acute event in a poorly controlled hypothyroid patient, such as infection, myocardial infarction, cold exposure, surgery, or the administration of sedative drugs, especially opioids. The presenting features frequently do not result in a coma, but rather with variable degrees of altered consciousness, such as confusion and lethargy. However, in rare instances, the initial presentation is with prominent psychotic features, termed "myxedema madness." If this is unrecognized, patients will progress to coma. The other major clinical findings will be of hypothermia, which needs to be assessed by manually examining the patient, in particular the hands (peripheries), as many automatic thermometers do not record subnormal temperatures.[62] The patient's vital signs will demonstrate marked hypotension and bradycardia (slow pulse) and blood tests will reveal marked hypoglycemia and hyponatremia (decreased serum sodium levels). Myxedema coma is a medical emergency, with a poor prognosis, requiring prompt hospitalization. The key aspects of treatment are replacement T4 and T3. In addition, prophylactic hydrocortisone 100 mg is administered intravenously (every eight hours) until adrenal insufficiency is excluded, as well as intensive supportive measures, including mechanical ventilation, fluids, and vasopressor drugs to correct hypotension, passive rewarming), and intravenous dextrose. Empirical antibiotic treatment is usually also given. Ongoing cardiorespiratory monitoring for arrhythmias is also mandated. The mortality rate, even with the best inpatient care, is 30–50%.[63]

Hyperthyroidism

Hyperthyroidism (also termed thyrotoxicosis) is defined as thyroid overactivity with consequent increased release and greater circulating levels of T3 and T4. Hyperthyroidism is common. The reported overall prevalence is about 3%, with men and women over 65 years having the highest prevalence, of which 50% are taking levothyroxine. In the National Health and Nutrition Examination Survey, there was a bimodal distribution based on age, with prevalence highest in those subjects aged 20–39 years and those aged older than 79 years.[53]

Causes

Exogenous Causes

- The use of *supraphysiologic doses of levothyroxine* that may be intentional, e.g., in patients' post treatment for thyroid malignancy in order to maintain suppression of serum TSH.
- *Amiodarone-induced thyrotoxicosis*.[64] Amiodarone is a class III antiarrhythmic agent (Vaughan Williams' classification) that blocks the potassium channels of the atrial, nodal cardiac muscle cells and the ventricular tissues (which coordinate the heartbeat). Its main effect is to prolong repolarization of the cardiac muscle and is indicated for the treatment and prevention of ventricular fibrillation and ventricular tachycardia.[65,66] It causes both hypothyroidism and hyperthyroidism due to its high iodine content and its direct toxic effect on the thyroid.[67]

Endogenous Causes

- *Graves' disease*, a "classic" autoimmune condition, is the most common cause in young patients. It features the development of autoantigenic serum immunoglobulin (Ig) G antibodies that bind to the TSH receptors in the thyroid, thus stimulating thyroid hormone overproduction and secretion. Other autoimmune antibodies develop concurrently, similar to those seen in autoimmune hypothyroidism, including antibodies to thyroid peroxidase (TPO) and thyroglobulin antibodies. These can occur in up to 80% of cases and result perversely in hypothyroidism.
- *Toxic nodular goiter* (solitary or multinodular) with autonomous production and release of T3 and T4. Common in the elderly population.[68]
- *Subacute thyroiditis* (also known as subacute granulomatous thyroiditis, or de Quervain's thyroiditis) of likely viral etiology. Its main feature is painful goiter.
- *Postpartum thyroiditis* (see earlier).

Clinical Features

- *Eye signs*. Lid lag and "stare," which can occur with hyperthyroidism of any cause. However, there are other features that are distinct with Graves' orbitopathy (described later).
- *Skin*. Graves' dermopathy is rare and can occur on any extensor surface. Pretibial myxedema is the most commonly described and is an infiltration of the skin on the shin. Thyroid acropachy is very rare and consists of clubbing and new periosteal bone formation of the fingers, causing marked swelling.
- *Excessive growth rate/velocity*. Common in children together with weight gain or behavioral problems, such as hyperactivity.
- *Cardiovascular*. In the elderly, a frequent presentation is with atrial fibrillation, other types of tachycardias, and/or heart failure. TFTs are mandatory in patients with atrial fibrillation.

- *Apathetic thyrotoxicosis* in elderly patients presents with a clinical picture more like that of hypothyroidism.

Investigations

- *Serum TSH*, which will be reduced in hyperthyroidism (<0.05 mU/L).
- *Raised free T4 or T3* confirms the diagnosis; T4 is almost always raised, but T3 is a more sensitive indicator of hyperthyroidism.
- *TSH receptor–stimulating antibodies* (TSHR-Ab), which are 99% specific for Graves' disease.
- *Thyroid peroxidase (TPO) and thyroglobulin antibodies* are present in 80% of cases of Graves' disease.
- *Scintiscan ^{99}Tm* is useful if there is doubt as to the nature of the goiter.

Treatment

The hyperthyroidism of Graves' disease is treated by reducing thyroid hormone synthesis with an antithyroid drug, or by reducing the amount of thyroid tissue with radioiodine (^{131}iodine) treatment or thyroidectomy. Radioiodine is more often the first line of treatment in North America. Treatment approaches vary around the world, indicative that no single approach is ideal.

- *Radioactive ^{131}I* is given orally and, since iodine preferentially concentrates in the thyroid, the gland is then slowly destroyed over the course of months by the local radiotherapy effect. It is contradicted in pregnant and breastfeeding women.[69]
- *Antithyroid drugs*. The main drugs are the thionamides: propylthiouracil, carbimazole (not available in the United States), and the active metabolite of the latter, methimazole, which inhibits the function of TPO, reducing oxidation and organification of iodide. Remission rates are in the range of 30–60%. The major toxicity with these agents is a selective agranulocytosis, but this only occurs in less than 1% of patients.
- *Surgery*. Generally, this will be a total thyroidectomy. That is typically an option for patients who relapse after antithyroid drugs and who prefer this treatment to radioiodine.
- *Beta blockers*, in particular propranolol (20–40 mg every 6 h), or longer-acting selective β1 receptor blockers, such as atenolol, may be helpful to control the adrenergic symptoms, especially in the early stages before the antithyroid treatment is fully effective.
- *Surveillance*. 40–70% of patients may relapse following antithyroid drug therapy. Hypothyroidism occurs in most patients treated by drugs or radioiodine, and is inevitable after total thyroidectomy, hence these patients will need to be maintained on appropriately titrated, life-long replacement levothyroxine.

There is a small risk of increased overall mortality seen in patients with hyperthyroidism. The major long-term consequence of treatment for hyperthyroidism is an increased risk of osteoporosis. Marked TSH suppression leads to the development of atrial fibrillation, requiring cardiac rate-limiting drugs such as digoxin, with an attendant risk for thromboembolic stroke. Hence anticoagulant prophylaxis is required, either with either warfarin or increasingly with direct oral anticoagulants (DOACs; previously known as new oral anticoagulant agents or NOACs), which include apixaban (Eliquis®, Pfizer Medical), dabigatran (Pradaxa®, Boehringer Ingelheim, Ridgefield, CT, USA), rivaroxaban (Xarelto®, Janssen Pharmaceuticals, Titusville, NJ, USA), and edoxaban (Savaysa®, Daiichi Sankyo, Basking Ridge, NJ, USA).[70]

Graves' Orbitopathy

Graves' orbitopathy, also known as thyroid eye disease (TED), is an autoimmune inflammatory disorder of the orbit and periorbital tissues. It has distinctive clinical features, including the "stare," due to retraction of the upper eyelid with lid lag, and swelling of the orbit, causing an exophthalmos of variable severity. It occurs most commonly in association with Graves' disease, but can also be seen, albeit more rarely, with Hashimoto's thyroiditis, and even in patients who are otherwise euthyroid. The condition mostly affects the middle-aged (30–50 years of age) and predominantly women. Cigarette smoking raises the incidence eightfold. Annual incidence is 16 per 100,000 in women and 3 per 100,000 in men.[71] About 3–5% have severe disease with intense pain, and sight-threatening corneal ulceration or compression of the optic nerve. Unilateral orbitopathy can occur, but this is rare.

Initial treatment entails regulation of thyroid hormone levels and limitation of further damage to the eye, with the use of topical lubricants to prevent corneal damage. High-dose corticosteroids are effective in the initial reduction of the orbital inflammation. Radiotherapy has been trialed, but there is controversy as to its efficacy, as is the case with selenium, which is limited to the treatment of mild disease. As of January 2020, the US Food and Drug Administration (FDA) approved the use of the medication Tepezza® (teprotumumab-trbw; Horizon Therapeutics, Lake Forest, IL, USA) for the treatment of adults with TED.[72] Teprotumumab-trbw is a monoclonal antibody that binds IGF-1R. In TED pathogenic orbital disease, autoantibodies stimulate the orbital fibroblasts, resulting in the production of hyaluronan (a high molecular mass polysaccharide), causing the marked infiltration and so swelling of the eyelids and orbital tissues and resulting in the clinical features of TED. Teprotumumab blocks the stimulatory effects of pathogenic autoantibodies on the orbital fibroblasts.[73] Orbital decompression surgery is

indicated in severe eye disease to prevent blindness from optic nerve compression. Surgery is also indicated, after the incipient thyroid disease has been stable for six months, to improve function and to increase lubrication of the corneal surface to prevent corneal keratitis and for cosmesis.[74]

Thyroid Crisis

A thyroid crisis (or "thyroid storm") is a rare, life-threatening exacerbation of hyperthyroidism, which presents with fever, delirium, seizures, coma, vomiting, diarrhea, and jaundice. The mortality rate due to cardiac failure, arrhythmia, or hyperthermia is as high as 30%, even with treatment. Thyrotoxic crisis is usually precipitated by acute illness (e.g., stroke, infection, trauma, diabetic ketoacidosis), surgery (especially involving the thyroid), or radioiodine treatment of a patient with partially treated or untreated hyperthyroidism. In-hospital management is required, which includes intensive monitoring, supportive care, identification and treatment of the precipitating cause, and measures that reduce thyroid hormone synthesis; that is, large doses of antithyroid drugs, such as propylthiouracil. Propranolol is also given to reduce tachycardia and other adrenergic manifestations.

Thyroid Hormone Resistance

This occurs when the effectiveness of thyroid hormone is reduced and includes flaws in thyroid hormone action, transport, or metabolism. These are rare, in general have a genetic basis, and to date there is limited effective treatment. There are three main causes:

- Thyroid hormone cell membrane transport defect.
- Thyroid hormone metabolism defect.
- Thyroid hormone action defects.

Goiter (Thyroid Enlargement)

Goiter is a swelling of the anterior base of the neck resulting from an enlarged thyroid gland, which may be visible or only evident on palpation (see Table 22-9). In the United States where iodine deficiency is rare, up to 15% of the population have palpable goiter and as many as 50% microscopic nodules. In areas of the world where iodine deficiency is common and widespread, up to 90% of the population have significant goiter, termed "endemic goiter."[75,76]

The initial screening for thyroid dysfunction starts by examining and then palpating the thyroid gland for diffuse changes or nodules, which may be single or multiple. It is performed as part of a head and neck examination, which could be argued to be within the remit of dentists and represents a comprehensive examination of the patient, with a focus on dental disease, but in the context of potential disease of the related regional anatomy. The thyroid gland is examined with the patient's head extended to one side and with the examiner using the fingers of both hands to palpate the thyroid gland. Next, the patient is instructed to swallow, during which time the examiner can evaluate the anatomic extent of the lobules using the last three fingers of one hand. Note that the right lobule is usually larger than the left and that on relaxation, the thyroid outline cannot be observed in a healthy patient. Any anatomic abnormality of the thyroid gland is defined by its consistency, size, tenderness, and growth. If an abnormal finding is discovered, hormone and function and imaging studies, particularly ultrasound, needs to follow, with consideration for ultrasound-guided fine needle aspiration (FNA) biopsy.[77]

Table 22-9 Goiter: types and causes.

Diffuse
Simple • Physiologic (puberty, pregnancy)
Autoimmune **viral (infective) thyroiditis**
Large • Endemic
Nodular • Multinodular • Solitary (single) • Fibrotic (Riedel's thyroiditis)
Infiltration (miscellaneous) • Sarcoidosis
Malignancy • Adenomas • Carcinoma • Lymphoma

Thyroid Malignancies

Thyroid carcinoma is the most common malignancy of the endocrine system. Thyroid neoplasms can arise in each of the cell types that populate the gland, including thyroid follicular cells, calcitonin-producing C cells, lymphocytes, and stromal and vascular elements, as well as metastases from other sites (Table 22-10). Over the last 30 years, the incidence of thyroid cancer has increased from 4.9 to 14.3 cases per 100,000 individuals in the United States, with over 65,000 cases diagnosed in 2015.[78]

The risk factors for thyroid malignancy are (1) exogenous, namely exposure to radiotherapy of the head and/or head

Table 22-10 Thyroid malignancies.

Malignant Carcinoma (Arising from Thyroid Epithelium)	Prevalence
Follicular epithelial cell	
Papillary carcinomas	80–85%
Follicular carcinomas	2.5–7%
Poorly differentiated carcinomas	3–5%
Anaplastic (undifferentiated) carcinoma	1%
Neuroendocrine Tumor (Arising from the C [Calcitonin-Producing] Cells)	
Medullary thyroid cancer	<10%
Sporadic	
Familial	
Multiple endocrine neoplasia 2	
Lymphomas	1%
Metastases	
Breast, melanoma, lung, kidney	

Source: Data from Clayman, G. Thyroid cancer: thyroid cancer symptoms, diagnosis, and treatments. https://www.endocrineweb.com/conditions/thyroid-cancer/thyroid-cancer.

and neck region, which can include cranial radiotherapy, or from nuclear fallout following explosions of nuclear power plants, at Chernobyl (1986)[79] and more recently Fukushima (2011);[80] and (2) endogenous, specifically genetic abnormalities, patients who have a family history of papillary thyroid cancer in two or more first-degree relatives, multiple endocrine neoplasia type 2 (MEN 2), or other genetic syndromes associated with thyroid malignancy, such as Cowden's syndrome, familial polyposis, and Carney complex.[51]

Treatment

Papillary and Follicular Cancer

As most tumors are still TSH responsive, levothyroxine suppression of TSH is a mainstay of initial thyroid cancer treatment, followed by partial or near-total thyroidectomy (depending on the size of the tumor). This is followed by radioablation of the remnant thyroid gland (and tumor). Serum thyroglobulin is a sensitive marker of residual/recurrent thyroid cancer after initial treatment.

Anaplastic Thyroid Cancer

This is a poorly differentiated and aggressive cancer with a dismal prognosis, with most patients dying within six months of their diagnosis.

Medullary Thyroid Carcinoma

Medullary thyroid carcinoma (MTC) can be sporadic or familial, and accounts for about 5% of thyroid cancers. There are three familial forms of MTC: MEN 2A, MEN 2B, and familial MTC without other features of MEN.[81] The management of MTC is primarily surgical, as these tumors, unlike papillary and follicular thyroid cancer, do not take up radioiodine. Targeted small molecule tyrosine kinase inhibitors (TKIs) have shown benefit in large or recurrent disease. Examples include cabozantinib (sold in the United States as Cabometyx® and Cometriq®, Exelixis, Alameda, CA, USA), which inhibits the tyrosine kinases c-Met and vascular endothelial growth factor receptor 2 (VEGFR-2), and vandetanib (Caprelsa®, Sanofi Genzyme, Cambridge, MA, USA) acts as a kinase inhibitor of a number of cell receptors, mainly VEGFR, epidermal growth factor receptor (EGFR), and RET-tyrosine kinase.[82] The TKIs that target vascular growth receptors that have a role in angiogenesis have been shown to increase the risk of medication-related osteonecrosis of the jaws (MRONJ), particularly if given concurrently (fivefold increased MRONJ risk) with either a bisphosphonate or denosumab.[83] External radiation treatment has also been shown to provide benefit.

Thyroid Lymphoma

Treatment follows the guidelines used for other forms of lymphoma.

Stomatognathic Manifestations and Complications of Thyroid Disease

Both hypothyroidism and hyperthyroidism can occur in the same patient, because patients with clinically significant hypothyroidism are on replacement levothyroxine, and there is the risk of overtreatment and iatrogenic thyrotoxicosis. Similarly, patients on treatment for their hypothyroidism can develop marked hypothyroidism if they omit a number of doses, or if they are on an insufficient dose. Therefore, dentists need to be familiar with the symptoms and signs of both hypothyroidism and hyperthyroidism.

Patients with a history of thyroid cancer have probably undergone surgery or radioactive iodine therapy that can affect the adjacent regional tissues. Salivary gland dysfunction is one of the most common side effects of high-dose ^{131}I therapy for thyroid cancer.[84,85] ^{131}I targets the salivary glands, where it is concentrated and secreted into saliva. Dose-related damage to the salivary parenchyma results from ^{131}I irradiation and causes salivary gland swelling, pain, and hypofunction.[86–89]

Dental Management of the Patient with Thyroid Gland Disorders

Patients with autoimmune thyroid diseases (Hashimoto's thyroiditis) may also be susceptible to other autoimmune connective tissue disorders, including Sjögren syndrome. Antinuclear antibodies (ANAs) are found in one-third of

patients with autoimmune thyroid disorders, and Sjögren syndrome is found in nearly one-tenth of ANA-positive patients with autoimmune thyroid disorders.[90] The most common additional autoimmune disease identified in patients with primary Sjögren syndrome has been hypothyroidism;[91] also, there is a 7–17% prevalence of detectable thyroid antibodies in patients with Sjögren syndrome and rheumatoid arthritis.[92] Therefore, the thyroid patient who presents with signs and symptoms of hyposalivation and xerophthalmia should be evaluated for Sjögren syndrome.[84,93–95]

Hypothyroidism

In hypothyroidism, the orofacial findings include myxedema of the skin, an enlarged tongue (macroglossia), compromised periodontal health, delayed tooth eruption, delayed wound healing, and a hoarse voice. Salivary gland enlargement, changes in taste, and burning mouth symptoms have also been reported.[96,97]

Patients with hypothyroidism are susceptible to cardiovascular diseases; therefore, consultation with the patient's medical provider is indicated. Patients who have atrial fibrillation may be taking anticoagulants, depending on the severity of the arrhythmia. The use of epinephrine-containing local anesthetics is not contraindicated if the patient's hypothyroidism is well controlled, but in patients who have cardiovascular disease (congestive heart failure, atrial fibrillation) or who have uncertain control of their thyroid disease, local anesthetic and retraction cord soaked with epinephrine can be used, but cautiously. Hypothyroidism, especially if uncontrolled, can also lead to respiratory depression, so that patient positioning should be carefully considered when treating such patients. Consideration should be given to treating patients in a semi-upright position, with oxygen supplementation via nasal prongs or by the mask used in providing nitrous oxide to patients.

Hypothyroid patients are sensitive to CNS depressants and so these medications should be used carefully, with input from the patient's physician. For postoperative pain control, narcotic use should be limited, since there is greater susceptibility to these agents in patients with hypothyroidism. Patients with long-standing hypothyroidism may experience increased bleeding after trauma or surgery. The presence of excess subcutaneous mucopolysaccharides (due to decreased degradation) may impair the ability of small vessels to constrict if severed or traumatized, and this may result in increased postoperative hemorrhage from such infiltrated tissues, including mucosa and skin. Delayed wound healing may also occur due to decreased metabolic activity of the fibroblasts. However, a study of well-controlled primary hypothyroid patients who had been provided with dental implants demonstrated no significantly increased risk for implant failure when compared with matched normal controls.[98]

Hyperthyroidism

Hyperthyroidism can exacerbate the patient's response to dental pain and anxiety. Routine examination of the head and neck may disclose signs of thyroid disease, including changes in oculomotor function, protrusion of the eyes, enlargement of the thyroid, and so difficulty in swallowing, or of the tongue. The patient may demonstrate excessive sweating. The greatest concern is the development of thyrotoxicosis or a "thyroid storm," which includes symptoms of extreme irritability and delirium, hypotension, vomiting, and diarrhea.[99] It can be triggered by surgery, sepsis, and trauma. Emergency medical treatment is required for this condition. Epinephrine is contraindicated, and elective dental care should be deferred for patients who have hyperthyroidism and exhibit signs or symptoms of thyrotoxicosis.

Increased susceptibility to infection may develop as an adverse side effect of antithyroid agents, which can cause agranulocytosis or leukopenia. Propylthiouracil can also cause sialolith formation and can increase the anticoagulant effects of warfarin. Certain analgesics must be used with caution in these patients. Aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) may cause increased levels of circulating T4, leading to thyrotoxicosis. NSAIDs can also decrease the effect of beta blockers.[50] The use of epinephrine requires special consideration when treating hyperthyroid patients and those taking nonselective beta blockers.

DISORDERS OF THE ADRENAL GLANDS (CORTEX)

The normal adrenal glands weigh 6–11 g each, are located above the kidneys, and have their own rich blood supply.[100] Within the glands is the adrenal cortex, which produces three classes of corticosteroid hormones:

- Glucocorticoids (e.g., cortisol).
- Mineralocorticoids (e.g., aldosterone). Glucocorticoids and mineralocorticoids act through specific nuclear receptors, regulating aspects of the response to physiologic stress, and controlling blood pressure as well as electrolyte and glucose homeostasis.
- Adrenal androgen precursor (dehydroepiandrosterone [DHEA]) prohormones that are converted in peripheral target cells, principally the gonads, to become the sex steroids that, in turn, act via nuclear androgen and estrogen receptors. The sex steroids interact with androgen receptors that stimulate or control the development and maintenance of male characteristics, that is testosterone, or with the estrogen receptors, so regulating both the menstrual and the reproductive cycles.

Adrenal steroidogenesis occurs in a zone-specific fashion, with mineralocorticoid synthesis occurring in the outer zona

glomerulosa, glucocorticoid synthesis in the zona fasciculata, and adrenal androgen synthesis in the inner zona reticularis (Figure 22-12).

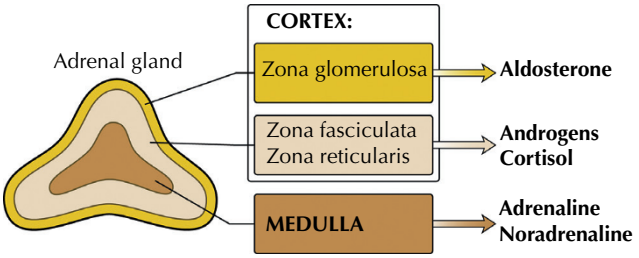


Figure 22-12 Adrenal steroidogenesis occurs in a zone-specific fashion. Mineralocorticoid synthesis (aldosterone) occurs in the outer zona glomerulosa. Glucocorticoid synthesis occurs in the zona fasciculate. Adrenal androgen synthesis occurs in the inner zona reticularis. The catecholamines (epinephrine and norepinephrine) are synthesized in the chromaffin cells of the adrenal medulla. *Source:* Kumar PJ, Clark ML (Eds.). *Kumar and Clark's Clinical Medicine*, 9th edn. Edinburgh: Saunders; 2017.

All the steroid hormones are derivatives of cholesterol (Figure 22-13). The steroidogenic pathway requires the import of cholesterol into the mitochondrion, a process initiated by the action of the steroidogenic acute regulatory (StAR) protein, which shuttles cholesterol from the outer to the inner mitochondrial membrane. Regulation of the production of glucocorticoids and adrenal androgens is under the control of the HPA axis (Figure 22-13).

Mineralocorticoids are regulated by the renin-angiotensin-aldosterone (RAA) system. Glucocorticoid synthesis is under inhibitory feedback control by the hypothalamus and the pituitary. Hypothalamic release of corticotrophin-releasing hormone (CRH) occurs in response to endogenous or exogenous stress. CRH in turn stimulates the release of ACTH by the cells of the anterior pituitary. ACTH is the pivotal regulator of cortisol synthesis, with additional short-term effects on mineralocorticoid and adrenal androgen synthesis. The release of CRH, and subsequently ACTH, occurs in a pulsatile fashion that follows a circadian rhythm, under the control of the hypothalamus. Reflecting this

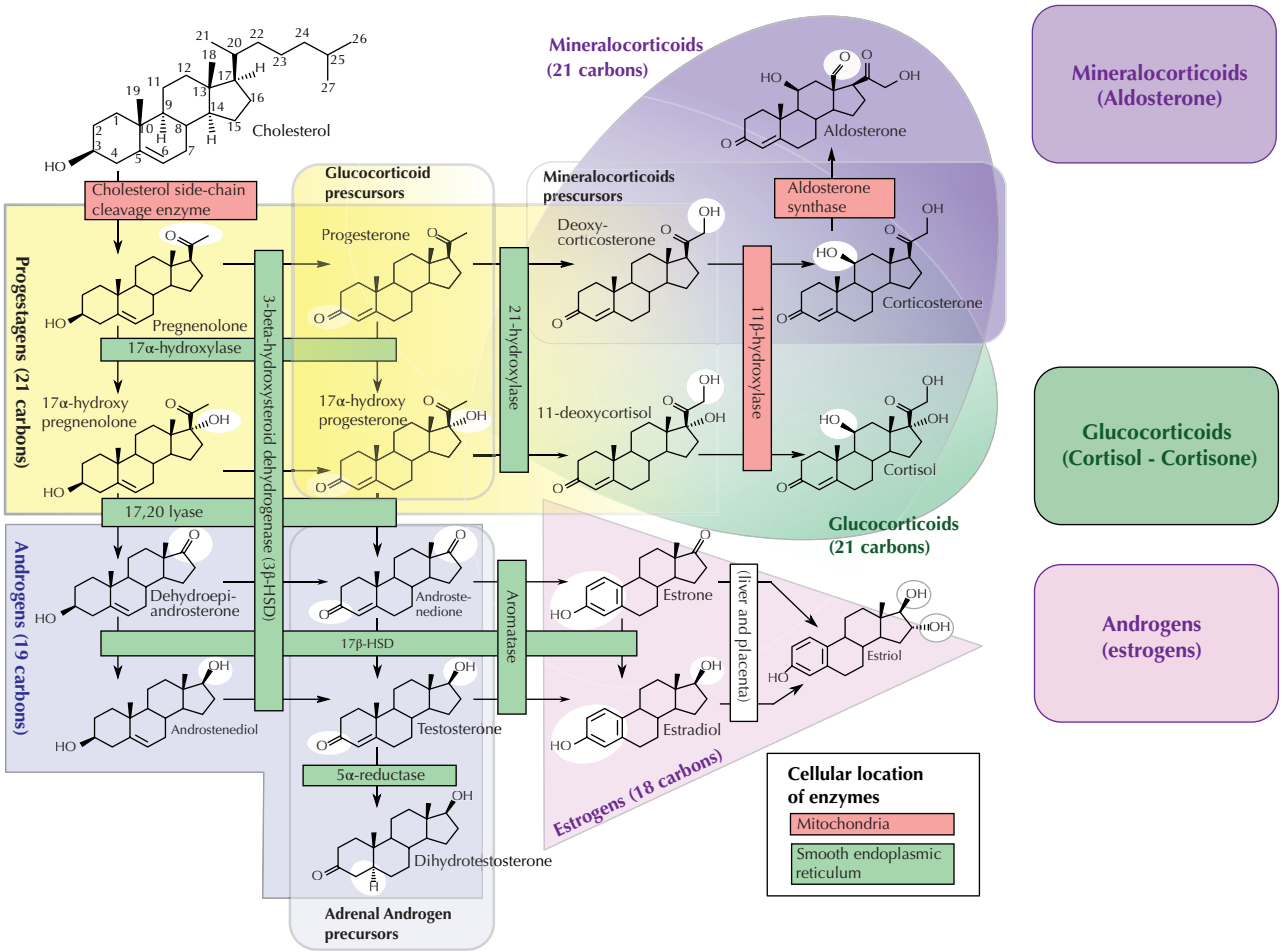


Figure 22-13 Adrenal steroidogenesis. Note how all the steroid hormones are derived from cholesterol. *Source:* https://commons.wikimedia.org/wiki/File:Steroidogenesis.svg. Creative Commons Attribution-Share Alike 3.0 Unported license.

pattern of ACTH secretion, adrenal cortisol secretion is also circadian, with peak levels in the morning and low levels in the evening

Diagnostic tests assessing the HPA axis makes use of the fact that it is regulated by negative feedback (Figure 22-1). Glucocorticoid excess is diagnosed by the dexamethasone suppression test. Dexamethasone, a potent glucocorticoid, suppresses CRH/ACTH and therefore lowers endogenous cortisol levels. If cortisol production is autonomous (e.g., from an adrenal adenoma), ACTH is already suppressed and the dexamethasone has little additional effect. If cortisol production is driven by an ACTH-producing pituitary adenoma, dexamethasone suppression is ineffective at low doses, but usually induces suppression at high doses. If cortisol production is driven by an ectopic source of ACTH, such as an ACTH-producing tumor, this is usually unaffected by dexamethasone suppression. Therefore, the dexamethasone suppression test is useful both in establishing the diagnosis of Cushing's syndrome (corticoid excess) and in differentiating the cause.[101] Conversely, to assess glucocorticoid deficiency, ACTH stimulation of cortisol production is used. The standard ACTH stimulation test involves administration of cosyntropin (Synacthen, a potent ACTH agonist) parenterally and the collection of blood samples at 0, 30, and 60 minutes to check the cortisol level.[102] A normal response is defined as a cortisol level >20 μg/dL or an increment of >10 μg/dL over baseline. Alternatively, an insulin tolerance test (ITT) can be used to assess adrenal insufficiency.

Mineralocorticoid production is controlled by the RAA regulatory cycle, which is initiated by the release of renin from the juxtaglomerular cells in the kidney, resulting in cleavage of angiotensinogen to angiotensin I in the liver. Angiotensin-converting enzyme (ACE) cleaves angiotensin I to angiotensin II, which binds and activates the angiotensin II receptor type 1 (AT1 receptor), resulting in increased aldosterone production and vasoconstriction. Aldosterone enhances sodium retention and potassium excretion, and increases renal arterial perfusion pressure, which in turn regulates renin release. As mineralocorticoid synthesis is primarily under the control of the RAA system, disorders of the hypothalamic-pituitary axis generally do not adversely affect adrenal gland synthesis of aldosterone.

Cushing's Syndrome (Glucocorticoid Excess)

Cushing's syndrome reflects a constellation of clinical features that result from the chronic effects of glucocorticoid excess, of any etiology and any source. Cushing's syndrome is rare, with an annual incidence of 1–2 per 100,000 population. The disorder can be ACTH dependent (e.g., pituitary corticotrope adenoma) or ACTH independent (e.g., adrenocortical tumor). Overwhelmingly, the medical use of glucocorticoids is the commonest cause of Cushing's syndrome. Only 10% of patients with Cushing's syndrome have a primary—that is, adrenal—cause of their disease.[103] The term "Cushing's disease" is specific to glucocorticoid excess caused by a pituitary adenoma secreting ACTH.

Ectopic ACTH production is predominantly caused by occult carcinoid tumors, most frequently in the lung, but also in the thymus or pancreas. Advanced small cell lung cancer can also cause ectopic ACTH production.[104]

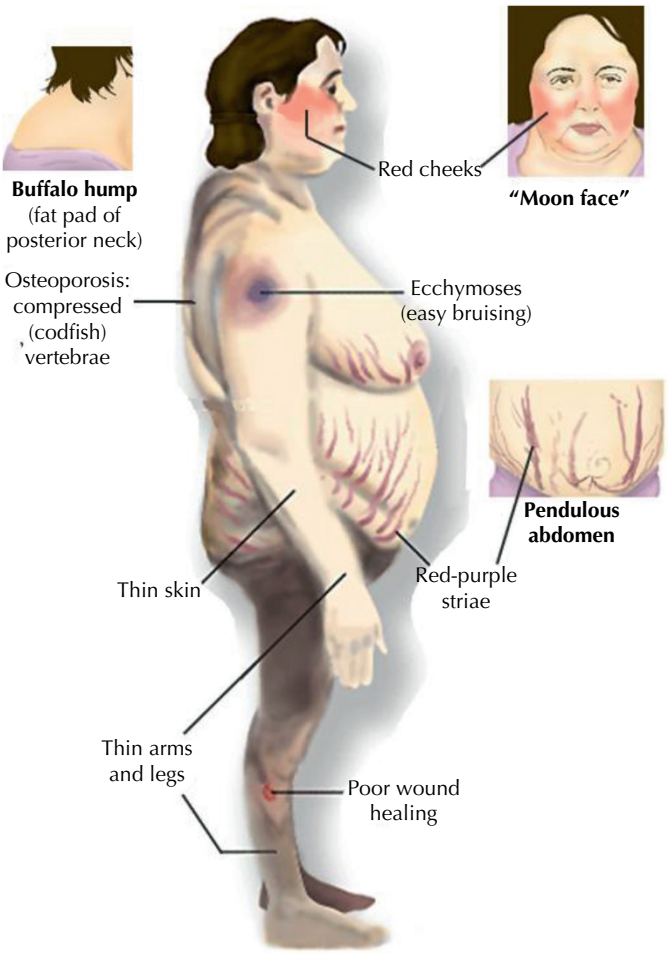
Clinical Manifestations

Given that glucocorticoids (see Table 22-11) affect almost all cells of the body, the signs of cortisol excess impact multiple physiologic systems. In addition, excess glucocorticoid secretion overcomes the ability of a key kidney enzyme system (11 β-hydroxysteroid dehydrogenase type 2 or 11β-HSD2) to rapidly inactivate cortisol to cortisone. Cortisone has minimal mineralocorticoid activity, whereas cortisol has

Table 22-11 Major actions of glucocorticoids.

Organ/ Physiologic System	↑ Increased or Stimulated	↓ Decreased or Inhibited
Metabolic	↑ Gluconeogenesis ↑ Glycogen deposition ↑ Protein catabolism ↑ Fat deposition	↓ Protein synthesis
Renal (Kidneys) System	↑ Sodium retention ↑ Potassium loss ↑ Uric acid production	↓ Free water clearance
Hematologic System	↑ Circulating neutrophils	↓ Host response to infection, delayed hypersensitivity response ↓ Lymphocyte transformation, circulating lymphocytes, circulating eosinophils

Symptoms
Proximal myopathy (muscle weakness upper arms/legs) Back pain
Mental State Depression Psychosis
Endocrine Delayed growth (children) **Elevated blood glucose levels**



Signs
Plethoric (red) facies Fat Redistribution Weight gain **"Buffalo Hump"**
Dermatological Hirsutism (hair growth) Acne Frontal balding (women) **Thin (atrophic) skin** **Easy bruising** Poor wound healing **Purple-red striae**
Cardiovascular **Hypertension** Edema (peripheries)
Renal Polyuria with polydipsia Glucosuria
Musculoskeletal Proximal myopathy (muscle weakness of upper arms/legs **Osteoporosis** Pathological fractures Kyphosis

Figure 22-14 Hypercortisolism—Cushing's syndrome. Bold type indicates symptoms or signs of greater diagnostic significance.

some degree of mineralocorticoid action, which manifest as diastolic hypertension, hypokalemia, and edema. Excess glucocorticoids also interfere with central regulatory systems, leading to suppression of gonadotropins with subsequent hypogonadism and amenorrhea, and suppression of the hypothalamic-pituitary-thyroid axis, resulting in decreased TSH secretion.

The diagnosis of Cushing's syndrome should be considered when the following key clinical features are evident in the patient (see Figure 22-14): fragility of the skin, with easy bruising and broad (>1 cm), purplish striae, and signs of proximal myopathy, with the patient struggling to stand up from a chair (without the use of hands). Patients with Cushing's syndrome may develop marked hypercoagulopathy, so are at acutely increased risk of deep vein thrombosis and subsequent pulmonary embolism. Psychiatric symptoms of marked anxiety and/or depression are also common, but acute paranoia or frank psychosis may also occur.[101]

Overt untreated Cushing's syndrome is associated with a poor prognosis. In ACTH-independent disease, treatment consists of surgical removal of the adrenal tumor. In Cushing's syndrome, the treatment of choice is selective removal of the pituitary corticotrophic-producing tumor, usually via a transsphenoidal approach.

Conn's Syndrome (Mineralocorticoid Excess)

Hyperaldosteronism, the excessive release of the principal mineralocorticoid, aldosterone, typically presents as hypertension, given the adverse effects on the renin-angiotensin system that so powerfully controls renal perfusion and homeostasis, and blood pressure. The commonest cause is primary hyperaldosteronism, excess production of aldosterone by the adrenal zona glomerulosa, typically occurring with bilateral micronodular adrenal hyperplasia. Infrequently, Conn's syndrome occurs due to an adrenocortical carcinoma.

The clinical hallmark of mineralocorticoid excess is hypokalemic hypertension, but not hypernatremia, with the serum sodium tending to be normal due to the concurrent fluid retention, which in some cases can lead to marked peripheral edema. Severe hypokalemia can be associated with muscle weakness, overt proximal myopathy, or, in severe cases, hypokalemic paralysis, or tetany.[105] Diagnostic screening for mineralocorticoid excess is not currently recommended for all patients with hypertension, but should be considered in hypertensive patients younger than 40 years, treatment-refractory hypertension, hypokalemia, or the finding of an adrenal mass. The accepted screening test is concurrent measurement of plasma renin and aldosterone with subsequent calculation of the aldosterone–renin ratio, but the serum potassium needs to be normalized prior to testing.

With the diagnosis of hyperaldosteronism, CT imaging of the adrenal glands is needed. The treatment provided is dependent on the patient's age and fitness for surgery. Laparoscopic adrenalectomy is the preferred approach. Medical treatment, which can also be considered prior to surgery to avoid postsurgical hypoaldosteronism, is usually with the mineralocorticoid receptor antagonist spironolactone.[106]

Addison's Disease (Adrenal Insufficiency)

The US prevalence of adrenal insufficiency (Table 22-12) is 5 in 10,000 in the general population. Disorders of the hypothalamic-pituitary axis are more frequent, with a prevalence of 3 in 10,000, whereas primary adrenal insufficiency has a prevalence of 2 in 10,000, with about half of cases due to genetic causes (e.g., congenital adrenal hyperplasia). Primary adrenal insufficiency is most commonly caused by autoimmune destruction of the adrenal gland, with some 60–70% developing adrenal insufficiency as part of an autoimmune polyglandular syndrome (APS). APS1, an autosomal recessive disorder also termed APECED (autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy), is the underlying cause in 10% of patients affected by APS.[107] These patients invariably develop chronic mucocutaneous candidiasis, which usually manifests in childhood and precedes adrenal insufficiency by years or decades. Coincident autoimmune-induced endocrinopathies most frequently include thyroid autoimmune disease, vitiligo, and premature ovarian failure. Less commonly, T1DM and pernicious anemia (with consequent vitamin B_{12} deficiency) may occur. Rare causes of adrenal insufficiency involve destruction of the adrenal glands as a consequence of infection, with tuberculous adrenalitis still a frequent cause of disease in developing countries. Hemorrhage, or more rarely bilateral bulky metastatic infiltration with replacement of the adrenal glands, can also result in hypoadrenalism.

The commonest cause of adrenal insufficiency is iatrogenic, arising from suppression of the HPA axis as a consequence of exogenous glucocorticoid treatment (see Tables 22-13 and 22-14).[108] This has a reported prevalence of some 0.5–2% of the population in developed countries. Secondary adrenal insufficiency is the consequence of dysfunction of the hypothalamic-pituitary component of the HPA axis. Excluding iatrogenic impairment of the HPA axis (exogenous corticosteroid use), the majority of cases are caused by pituitary or hypothalamic tumors, or their treatment by surgery or radiotherapy.

In principle, the clinical features of primary adrenal insufficiency (Figure 22-15) are characterized by the loss of both glucocorticoid and mineralocorticoid secretion. In contrast, in secondary adrenal insufficiency only glucocorticoid deficiency is evident, as the adrenal itself is intact and can still be regulated by the RAA system. Adrenal androgen secretion is disrupted in both primary and

Table 22-12 Adrenal insufficiency (hypoadrenalism): classification.

1. Primary Adrenal Insufficiency (Addison's Disease)	2. Secondary Adrenal Insufficiency
a. Destruction of adrenal gland	**a. Hypopituitarism**
Immune (autoimmune)	Due to hypothalamic-pituitary disease (intracranial brain tumors)
"Idiopathic"	**b. Suppression of the hypothalamic-pituitary-adrenal (HPA) axis**
Surgical removal	Exogenous glucocorticosteroids
Infection (tuberculosis, *Mycobacterium avium*–intercellular complex, fungal, viral)	Endogenous adrenocorticotropic hormone/steroid from a tumor
Hemorrhage (anticoagulants)	**c. Endogenous glucocorticosteroid resistance**
b. Metabolic failure of hormone production	Severe acute illness (shock/ICU admission)
Congenital adrenal hyperplasia	
Enzyme inhibition (ketoconazole)	
Cytotoxic agents (Mitotane)	

Table 22-13 Therapeutic use of corticosteroids.

Nervous system	• Cerebral edema • Raised intracranial pressure
Respiratory	• Angioedema • Anaphylaxis • Asthma • Sarcoidosis • Obstructive airway disease
Endocrine	• Replacement therapy (Addison's, pituitary disease, adrenal hypoplasia) • Graves' ophthalmopathy
Gastrointestinal	• Inflammatory bowel disease (ulcerative colitis, Crohn's disease) • Orofacial granulomatosis
Liver	• Chronic active hepatitis • Transplantation (antirejection)
Renal	• Nephrotic syndrome • Vasculitides • Transplantation (antirejection)
Rheumatology	• Systemic lupus erythematosus • Polyarteritis • Temporal arteritis • Rheumatoid arthritis
Musculoskeletal	• Polymyalgia rheumatica • Myasthenia gravis
Skin/oral medicine	• Dermatitis • Pemphigus • Oral dermatoses
Hematology	• Malignancy • Hemolytic anemia • Idiopathic thrombocytopenic purpura • Chemotherapy-related nausea

secondary adrenal insufficiency. Hypothalamic-pituitary disease can lead to additional clinical manifestations due to the involvement of other endocrine axes, or visual impairment with bitemporal hemianopia caused by compression of the optic chiasma. Iatrogenic adrenal insufficiency caused by exogenous glucocorticoid suppression of the HPA axis and its abrupt cessation can cause all of the symptoms associated with glucocorticoid deficiency, but the patient will appear cushingoid from the preceding "overexposure" to glucocorticoids.

Acute adrenal insufficiency usually occurs after a prolonged period of nonspecific complaints and is more frequently observed in patients with primary adrenal insufficiency, due to the loss of both glucocorticoid and mineralocorticoid secretion. The associated postural hypotension is a "red flag," as the patient may then progress to hypovolemic shock. Adrenal insufficiency may also mimic the features of an acute abdomen with abdominal tenderness, nausea, vomiting, and fever. An adrenal crisis can be triggered by an intercurrent illness, surgery, or other stress.[109]

Table 22-14 Glucocorticoid equivalencies.

Glucocorticoid	Equivalent Dose (mg)	Potency	Biologic Half-life (h)
Short-Acting Corticosteroids			
Cortisol	20.0	1.0	8–12
Cortisone	25.0	0.8	8–12
Intermediate-Acting			
Prednisone	5.0	4.0	18–36
Prednisolone	5.0	5.0	18–36
Triamcinolone	4.0	5.0	18–36
Methylprednisolone	4.0	5.0	18–36
Long-Acting			
Dexamethasone	0.75	30	36–54

Source: Data from Nicolaides NC, Pavlaki AN, Maria Alexandra MA, et al. Glucocorticoid therapy and adrenal suppression. Updated 2018. In: Feingold KR, Anawalt B, Boyce A, et al. (Eds.), *Endotext*. South Dartmouth, MA: MDText.com. https://www.ncbi.nlm.nih.gov/books/NBK279156/.

The diagnosis of adrenal insufficiency is established by the short cosyntropin test (Synacthen), a safe and reliable tool with excellent diagnostic sensitivity. The ITT is an alternate, but can be hazardous to the patient, and requires supervision by a specialist physician.

Acute adrenal insufficiency requires immediate rehydration (1 L/hour of saline infusion) with cardiac monitoring and glucocorticoid replacement by bolus injection of 100 mg hydrocortisone, followed by further hydrocortisone supplementation (100–200 mg hydrocortisone over the course of 24 h). Mineralocorticoid replacement can wait until the daily hydrocortisone dose has been reduced to <50 mg, because at higher doses the hydrocortisone provides sufficient stimulation of the mineralocorticoid receptors.

Glucocorticoid replacement (Table 22-15) for the treatment of chronic adrenal insufficiency should be administered at a dose that replaces the physiologic daily cortisol production, typically orally administered hydrocortisone at a dose of 15–25 mg, in two divided doses: 10–20 mg in the mornings and 5 mg in the evenings, mimicking the natural circadian levels of cortisol.

Mineralocorticoid replacement in primary adrenal insufficiency is achieved by the use of 100–150 μg of fludrocortisone. Its efficacy is assessed by measuring the blood pressure, while both sitting and standing, to detect a postural drop indicative of hypovolemia, and assessing serum sodium, potassium, and plasma renin levels. Adrenal androgen replacement is an option for patients with a lack of energy, or with features of androgen deficiency, such as loss of libido.

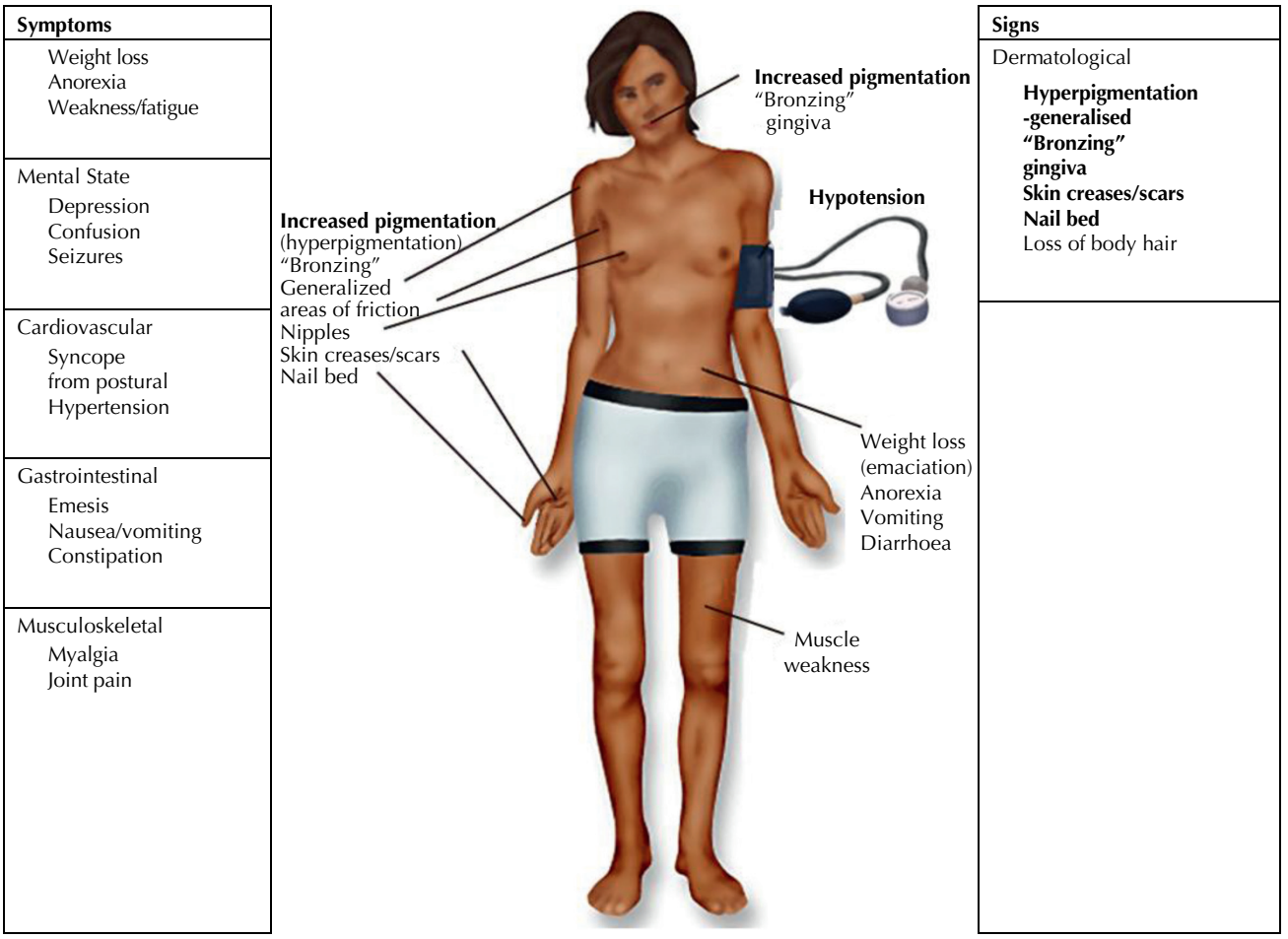


Figure 22-15 Hypoadrenalism—Addison's disease. Bold type indicates symptoms or signs of greater diagnostic significance. *Source:* Letters to the Editor. Medical mystery—the answer revealed. *N Engl J Med*. 1998;338(4):266–268.

Table 22-15 Indications for corticosteroid use.

Therapeutic Uses	Supplementation for Hypoadrenalism
Anti-inflammatory/immune suppression • Topical • Intralesional • Inhaled • Intra-articular • Systemic (PO/parenteral) • Prevention of surgical edema (wisdom teeth removal)	Hydrocortisone (corticosteroid): dose dependent on patient's weight and age • 20 mg am/10 mg pm (or dexamethasone 5 mg/day) + fludrocortisone (mineralocorticoid) 0.05–0.20 mg/day +/– presence of stressors: illness, infection, surgery, and/or pregnancy
Antineoplastic (hematologic malignancy)	**3. Replacement ("Stress") Corticosteroids**
Antiemetic (chemotherapy) Palliative care	HPA axis impairment (exogenous corticosteroid use): • Primary hypoadrenalism

po; per oral

Pheochromocytoma

This is an adrenal tumor that produces epinephrine, norepinephrine, or both catecholamines. Patients are hypertensive, with headache, sweating, tachycardia, palpitations, and pallor. Occasionally, these can be syndromic, as part of Multiple Endocrine Neoplasia Syndrome Type 2B (MEN2B) presenting with a marfanoid habitus, high arched palate, neuromas (of the tongue, buccal mucosa, lips, conjunctivae, and eyelids), and corneal nerve thickening. The diagnosis of pheochromocytoma is confirmed by measuring urinary and plasma catecholamine levels.[110]

Stomatognathic Manifestations and Complications of Disorders of the Adrenal Gland

Hyperadrenocorticism (Glucocorticoid Excess or Cushing's Syndrome)

The primary orofacial feature of Cushing's syndrome is a round, moon face due to muscle wasting and accumulation of fat. Surface capillaries in the face and other skin regions become fragile, rendering them readily susceptible to hematomas after mild trauma. The facial skin has a ruddy color that simulates "glowing health"; acne and excessive facial hair (hirsutism) are also commonly seen. Long-standing Cushing's syndrome in children produces delayed growth and development, including of the skeletal and dental structures. Many of the systemic findings of Cushing's syndrome are similar to those seen in patients on moderate- to high-dose glucocorticoid therapy, and these patients are considered to be immunosuppressed. Therefore, oral signs and symptoms of immunosuppression can be seen, including oral candidiasis, recurrent herpes labialis and herpes zoster infections, gingival and periodontal diseases, and impaired wound healing.

Hypoadrenocorticism (Glucocorticoid Deficiency or Addison's Disease)

The primary orofacial feature of Addison's disease is unusual skin pigmentation, most intensely of the sun-exposed areas due to ACTH stimulation of the melanocytes. Facial freckles and moles appear darker, in addition to the development of a tan-like complexion ("bronzing" of the skin and sometimes of the oral mucosa), which does not fade on cessation of sunlight exposure. The mucocutaneous junctions undergo increased pigmentation, including the lips, but hyperpigmentation can also involve the intraoral mucosal surfaces, such as the gingival margins, buccal mucosa, palate, and lingual surface of the tongue. The oral pigmentations appear as irregular spots that range from pale brown to gray or black.[111]

Dental Management of Patients with Adrenal Gland Disorders

Hyperadrenocorticism (Glucocorticoid Excess or Cushing's Syndrome)

Dental management of the patient with Cushing's syndrome must take into consideration concomitant medical conditions that can include hypertension and heart failure, depression or psychosis, as well as DM and osteoporosis. Patients will present with easy bruising of the skin, impaired wound healing, and the infective consequences of immunosuppression. Prophylactic antibiotic coverage should be considered prior to surgery (extractions) for active dentoalveolar infections.

Assessment of the ability to withstand stress is an essential component of treatment planning for patients with Cushing's syndrome and other patients who have been on long-term moderate- to high-dose glucocorticoid therapy (see Table 22-12). Stress may be induced by an invasive surgical procedure, the onset of infection, an exacerbation of an underlying disease, or a serious life event, such as the death of a family member.[112] When normal individuals undergo stress, the plasma cortisol levels can double, due to the inherent ability of the adrenal glands to significantly increase cortisol production. But, in a patient with adrenal insufficiency, adrenal function is inadequate to produce sufficient cortisol in response to stress. Consequently, the patient may experience severe hypotension, with cardiovascular events such as stroke, coma, and death. Patients with established severe adrenal insufficiency usually require premedication with oral or intramuscular glucocorticoids before an invasive procedure. Dosages must be agreed upon with the patient's physician; a frequent regimen is to double the daily dose of oral glucocorticoids the day before the surgery and on the day of surgery.[113]

Hypoadrenocorticism (Glucocorticoid Deficiency or Addison's Disease)

Dental management is similar to that for the patient who has taken long-term moderate to high doses of glucocorticoids (see earlier), since Addison's disease is frequently treated with exogenous glucocorticoids. The oral health practitioner must be able to recognize and provide initial management of an acute adrenal crisis (intramuscular or intravenous hydrocortisone) when treating these patients.[114]

Use of Replacement Corticosteroid Therapy ("Stress Steroids" or "Steroid Cover")

Cortisol (hydrocortisone) is essential to maintain vasomotor tone, and so normal blood pressure, by sensitizing the alpha-adrenergic receptors (alpha 1A, 1B, and 1D receptors) of the vasculature to circulating epinephrine and norepinephrine

Table 22-16 Dental procedures and recommended replacement corticosteroids.

Risk Category	Dental Procedure	Hydrocortisone	Prednisone	Dexamethasone
Negligible	• Nonsurgical & in chair +/- local anesthetic	Nil	Nil	
Mild	• Minor oral surgery • Minor periodontal surgery } in the dental chair			Nil
Moderate to severe	• Major oral or periodontal surgery—multiple extractions/implants • Procedure >60 mins • Significant blood loss • general anesthetic/intubation	50–100 mg day of surgery *and 24 hours* afterward	10–20 mg within 2 hours of procedure	~2–4 mg (long-acting) >48 hours
Monitoring	• BP (100/60) systolic >100; diastolic >60 ➔ if *lower* give fluids (5% dextrose saline)			

and increasing catecholamine release from the adrenal cortex. If insufficient cortisol is produced at times of marked physiologic stress, this can result in vasodilation, reduced cardiac return, and potential hypotensive cardiac shock, leading to collapse and death. Significant physiologic stressors include severe infection and/or injury; that is, surgery and intubation associated with general anesthesia.[115–117]

Iatrogenic adrenal insufficiency is caused by suppression of the HPA axis due to exogenous glucocorticoid therapy. The mean cortisol production rate is 5.7 mg/m^2/day, or about 10 mg/day (equal to 2.5 mg of prednisone or 0.5 mg of dexamethasone) (see Table 22-15).[118] Body surface area (BSA) is used to calculate the dose of a drug relative to the patient's "ideal" body weight, resulting in a dose per meter squared (m^2). The BSA is a better indicator of the patient's "ideal" body weight because it is less affected by abnormal adipose mass, and this is useful when giving drugs with a narrow therapeutic safety index, such as chemotherapy agents. Of the various formulations, the Mosteller equation is simpler and considered more accurate:

$$\mathrm{BSA}\left(\mathrm{m2}\right)=\frac{\sqrt{height\left(cm\right)\times weight\left(kg\right)}}{3600}$$

Therefore, exogenous glucocorticoids that exceed the mean level of cortisol production can result in suppression of the HPA axis, as well as atrophy of the adrenal glands. Consequently, at times of acute physiologic (and possibly psychologic stress), the now atrophied adrenal gland is unable to produce sufficient cortisol for the affected patient to respond appropriately to stress. Historically this resulted in the so-called Rule of Twos, in which a patient was thought to be susceptible to an impaired response to physiologic stress, due to adrenocorticoid suppression from exogenous corticosteroids used for the medical treatment of predominantly immune-related or inflammatory conditions. The Rule stated that if a patient had taken glucocorticoids in excess of 20 mg of cortisone, continuously for 2 weeks (or more), within 2 years of the date/day of their dental treatment, this patient needed supplementary steroids prior to their dental treatment.[119] What is now very clear is that the published evidence has concluded that supplementary steroids ("steroid cover") are not indicated for dental procedures done in the dental chair and facilitated by means of local anesthesia, for patients using therapeutic corticosteroids. The evidence for using such "stress steroids" is at best equivocal for more major dental (surgical) procedures. For patients who have recently (within 2 years) ceased supraphysiologic corticosteroid therapy, the evidence is again considered to be equivocal.

Thus, in assessing the need for a patient with hypoadrenalism to receive preprocedural supplemental corticosteroids (Table 22-16), the essentials still need to be applied: careful patient assessment and evaluation, including taking a detailed medical history, with particular attention to recent surgery and how the patient coped with the procedure.[120–122] However, for patients undertaking dental procedures utilizing oral or intravenous sedation with potent short-acting benzodiazepines (e.g., midazolam) to abrogate the psychologic stresses associated with invasive dental treatment, this intended blunting of the emotional stress response may blunt the physiologic stress response. Therefore, for those patients with primary hypoadrenalism or on long-term supraphysiologic doses of corticosteroids having dental treatment aided by means of oral or intravenous sedation, supplementary pre- or periprocedural "stress steroids" should be considered and possibly provided.[123]

GONADS AND GONADAL DYSFUNCTION

The gonads, like most other endocrine organs, are incorporated into an endocrine axis: the hypothalamic-pituitary-gonadal (HPG) axis. The physiologic function and regulation of the HPG axis, especially in women, is complex and

changes dramatically over a lifetime. The hypothalamic hormone in the HPG axis is gonadotropin-releasing hormone (GnRH). GnRH is released in a complicated pulsatile fashion that varies widely in a person's lifetime and is significantly different between men and women. The general principles of stimulation and feedback inhibition apply to the HPG axis (see Figures 22-4 and 22-5); however, this axis is complicated by two issues: GnRH is pulsatile, and the pituitary makes two hormones, LH and FSH. In the male, LH stimulates testosterone production from the Leydig cells of the testicles, and FSH stimulates sperm production by the Sertoli cells. In females, FSH stimulates maturation of the ovarian follicle, and LH causes "luteinization," or maturation of the follicle into a corpus luteum, as well as the production of ovarian estradiol.

For both males and females, the HPG axis is relatively dormant before the onset of puberty. The onset of puberty in girls occurs approximately 2 years before that of boys. In girls, the average age at which breast development starts is 10.5 years, and menses starts at about 12 years. In boys, the peak growth rate and beginning of voice change are about the age of 14 years, whereas facial hair appears on average at the age of 15 years. In men, from late puberty until about age 60 years, the serum testosterone levels are relatively constant and begin to decline gradually thereafter. In women, serum estradiol levels vary widely over the course of the menstrual cycle, but after the onset of menopause (which occurs on average at the age of 50 years), serum estradiol levels become very low and gonadotropin (LH and FSH) levels are elevated.

Precocious Puberty, Delayed Puberty, Hypogonadism, and Menopause

In both males and females, precocious puberty, delayed puberty, and hypogonadism are clinical diagnoses, made by early or late signs of secondary sexual differentiation or loss of sexual characteristics.[124] Pubertal development is measured clinically by a staging system developed by Tanner.[125] Puberty is generally considered precocious in boys if it starts before age 10 years and in girls before age 8.5 years, or delayed if there are no signs of sexual development by the age of 13 years in girls and 14 years in boys.[126]

Once a clinical diagnosis of gonadal dysfunction is established, the next step is to determine whether the pathophysiologic process is of the gonads (primary/end-organ disorder), pituitary (secondary endocrinopathy), hypothalamus (tertiary endocrinopathy), or, alternatively as in the case of precocious puberty, due to an ectopic (or exogenous) source of the hormone. Gonadal testing usually involves measuring the appropriate sex steroid (testosterone or estradiol) and the pituitary gonadotropins LH and FSH. The most common cause of precocious puberty in boys and girls is early onset of pituitary hormone production, termed "central precocious puberty." If the end-organ hormones are elevated and the gonadotropins are suppressed (gonadotropin-independent precocious puberty), this suggests primary (autonomous) gonadal dysfunction. Finally, the adrenal gland also produces androgens that can lead to early puberty in boys and masculinization in girls.

Premature ovarian failure heralded by the onset of menopause before the age of 40 years presents as "hot flushes." The most common associated problem is cessation or marked irregularity of the menstrual cycle. Hypogonadism in men presents with a loss of libido and decreased growth rate of facial hair, and can lead to osteoporosis and fractures; it is diagnosed by a low serum testosterone level. Premature ovarian failure is diagnosed by the early loss of menstrual cycles in the setting of an elevated serum FSH. Replacement of the primary gonadal steroid, testosterone or estradiol or one of its analogues, in men and women is straightforward. However, replacement of the missing hormone will not return fertility, which is often the major concern. If the gonad is still functional but disorder or loss of the relevant pituitary hormones leads to a loss of function, the pituitary hormones can then be replaced.

Oral Manifestations of Gonadal Disorders

Hypersecretion of female sex hormones commonly occurs in pregnancy. High levels of female sex hormones cause increased capillary permeability, increased susceptibility to the development of gingivitis (pregnancy gingivitis), gingival hyperplasia, and pyogenic granulomas (pregnancy tumor).[127] These factors may complicate preexisting periodontal disease. A decrease in gonadal hormones at menopause is associated with a decrease in salivary flow and salivary composition.[128] Postmenopausal women also have increased susceptibility to osteoporosis, so dental radiographs may demonstrate hypocalcified bone.[129]

Dental Management of Patients with Gonadal Disorders

Elective and stressful dental procedures should be avoided during the first trimester of pregnancy and the last half of the third trimester. The second trimester is the safest period to provide dental care during pregnancy. During this time, emphasis should be on prevention, maintenance of optimal oral health, and treatment of dental concerns that may lead to complications in late stages of pregnancy.[130] Injudicious use of medications should be avoided in pregnancy; choice of medication should be guided by FDA pregnancy classifications for prescription drugs to avoid those with possible teratogenic effects.[131]

Table 22-17 Type 1 versus type 2 diabetes mellitus (DM) characteristics.

	Type 1 DM	Type 2 DM
Prevalence (DM—all types)	<5–10%	>90–95%
Age (of onset)	Younger (<30 years of age)	Older (>30 years of age)
Weight	Lean	Overweight/obese
Symptom duration	weeks	Months/years/decades
Risk factors		
Ethnicity	Northern European	Asian, African, American Indian, Australian Aboriginal, Polynesian
Social/lifestyle	(?) uncertain	Obesity, sedentary lifestyle
Heredity	HLA-DR3 or DR4 (>90%)	No HLA linkage
Pathogenesis	Autoimmune disease	?
Ketonuria	Yes	No
Clinical	Insulin deficiency	Partial insulin deficiency, initially then increasing insulin resistance
	± ketoacidosis	± hyperosmolar state
	Insulin dependent	Need insulin with time as beta pancreatic cells fail
	Increased risk of hypoglycemia	Lower risk of hypoglycemia

DIABETES MELLITUS

DM encompasses a group of heterogeneous metabolic disorders with a common phenotype of persistent, abnormally elevated blood glucose levels (hyperglycemia) in association with dysregulation of carbohydrate, protein, and lipid metabolism (see Table 22-17). This persistent hyperglycemia (disordered glucose homeostasis) results from either a defect in the secretion of insulin from the pancreas, or resistance to the action of insulin by the body's cells, or both.[132] Hyperglycemia has been shown to affect almost all tissues in the body and is associated with significant complications of multiple organ systems, including the eyes, nerves, kidneys, and blood vessels. These complications are responsible for the high degree of morbidity and mortality seen in the diabetic population. In the United States (as in other Westernized countries), DM is the leading cause of end-stage renal disease (ESRD);[133] nontraumatic toe, foot, and lower limb amputation;[134] and adult blindness.[135]

Epidemiology

Worldwide, DM, in particular T2DM given that it accounts for 90–95% of all patients with DM, is now one of the most common noncommunicable diseases. It is the ninth leading cause of death in most high-income countries and there is substantial evidence that it is now also becoming epidemic in many low- and middle-income countries.[136] The main risk factor for DM, specifically T2DM, is obesity. Obesity is defined as a condition in which excess body fat has accumulated to the extent that it may have a negative effect on health, leading to reduced life expectancy and/or morbidity.[137–139] The incidence of DM rises as the population ages and the prevalence of obesity increases.[140,141] In the United States, for the period 2007–2010, the crude total prevalence of DM was estimated at 11.4% of the population over 20 years of age (data obtained by self-report of physician-diagnosed diabetes and exclude women who reported having diabetes during pregnancy).

Hormonal Control of Blood Glucose[142]

Plasma glucose levels are normally tightly regulated in health, confined to a range of 3.5–8.0 mmol/L (63–144 mg/dL), despite physiologic stressors of food, fasting, and exercise. The principal organ of glucose homeostasis is the liver, which absorbs and stores glucose (in the form of glycogen) in the postabsorptive state (after the intake of food), and releases glucose into the circulation between meals to meet the rate of glucose utilization (cellular respiration) by the peripheral tissues. The liver is also the site of gluconeogenesis ("new sugar formation"), whereby 3-carbon molecules

derived from the breakdown of fat (glycerol), muscle glycogen (lactate), and protein (e.g., alanine) are synthesized into the 6-carbon glucose molecule. About 200 g of glucose is produced and used each day. More than 90% of this is derived from the glycogen stores in the liver and from gluconeogenesis. The remaining 10% is derived from gluconeogenesis undertaken by the kidneys.

The brain is the major consumer of glucose, requiring up to 1 mg/kg bodyweight per minute (i.e., 100 g/daily in a 70 kg patient). Glucose uptake by the brain is obligatory and not dependent on insulin, with the glucose used for energy (cellular respiration) or oxidized to form carbon dioxide and water. Other tissues, namely the fat and muscle cells, are facultative consumers of glucose, which otherwise rely on fatty acid oxidation for their energy needs. Glucose taken up by muscle cells is stored as glycogen or broken down to lactate, which enters the circulation to become a major substrate for hepatic gluconeogenesis. Glucose is used by fat cells as a source of energy and as a substrate for triglyceride synthesis. Lipolysis is the breakdown of lipids by the hydrolysis of triglycerides into free fatty acids and glycerol. The resulting glycerol also serves as a substrate for hepatic gluconeogenesis.

Cell membranes, because of their polar lipid bilayer, are not readily permeable to glucose. Glucose transporters (GLUT) are a family of four, ubiquitous, specialized cell membrane proteins that facilitate the transport of glucose (and related hexoses) through the plasma membrane.[143] The glucose transporter responsible for the majority of glucose uptake by cells of the body is GLUT 4, which operates solely at the bidding of insulin. GLUT 4 is found on the cells of adipose tissue as well as skeletal and cardiac muscle, and glucose cannot enter these cells without the presence of insulin.

Insulin

Insulin is the key hormone involved in the storage and controlled release of the energy available from food. Insulin is a peptide hormone produced by the beta (islet) cells of the endocrine pancreas. After secretion, insulin enters the portal circulation and is transported to the liver, its prime target organ. Half of this insulin is taken up from the circulation and degraded by the liver, with the residue broken down in the kidneys.

Insulin is a major regulator of intermediate metabolism. Although its actions are modified by many other hormones, its importance lies in its differing actions in the fasting and postprandial states. In the fasting state insulin functions to regulate the release of glucose by the liver, and in the postprandial state it facilitates the uptake of glucose by fat and muscle. The effect of counter-regulatory hormones (namely glucagon, epinephrine, cortisol, and GH) is to cause a greater release of glucose from the liver and decrease the utilization of glucose by the fat and muscle cells, for a given level of insulin.

Glucagon

Glucagon is a peptide hormone synthesized and secreted from alpha cells of the islets of Langerhans, of the endocrine portion of the pancreas (Box 22-2). Glucagon acts to raise blood glucose levels (Figure 22-16), so the effect of glucagon is opposite to that of insulin (which lowers blood glucose levels). The pancreas releases glucagon when blood glucose concentrations fall critically low (Table 22-18). Glucagon generally elevates blood glucose levels by promoting gluconeogenesis and glycogenolysis in the liver. High blood glucose levels stimulate the release of insulin, which then allows glucose to be taken up and used by insulin-dependent tissues. Thus, glucagon and insulin are part of a feedback system that maintains blood glucose levels at a stable level. Glucagon also regulates the rate of glucose production through lipolysis.

Amylin

Amylin, or islet amyloid polypeptide (IAPP), is a 37-residue peptide hormone. It is co-secreted with insulin from the pancreatic beta cells at a ratio of approximately 100:1. Amylin functions as a synergistic partner to insulin. The overall effect is to slow the rate of appearance of glucose in the blood. After eating, amylin causes a coordinated slowing of gastric emptying, the inhibition of digestive secretions (gastric acid, pancreatic enzymes, and bile), and the induction of satiety that results in a reduction in food intake. Blood glucose levels are also reduced by inhibiting secretion of the gluconeogenic hormone glucagon. Collectively, these actions reduce the total demand for insulin. These actions are largely mediated by the glucose-sensitive part of the brain stem, the *area postrema*,

Box 22-2 Glucagon (Peptide Hormone) versus Glycogen (Polysaccharide)

Glucagon is secreted by the pancreas, is a peptide hormone that raises blood glucose levels, and its effect is *opposite that of insulin* (insulin lowers blood glucose levels).

Glycogen is a multibranched polysaccharide of glucose that serves as secondary energy storage (the primary energy stores being fats held in adipose tissue). Glycogen is made and stored primarily in the hepatocytes and the muscles.

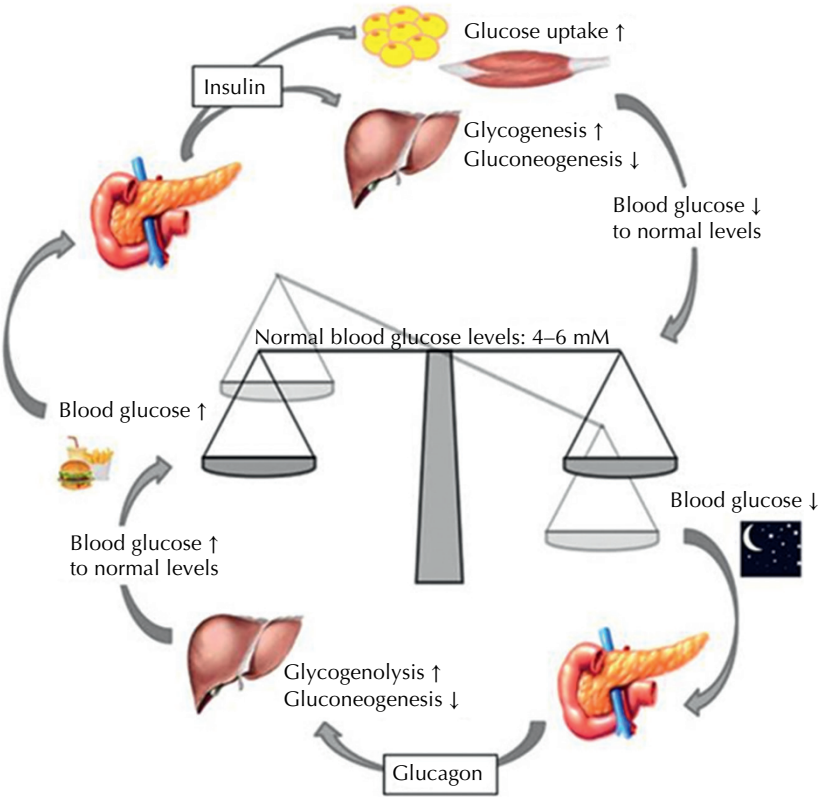


Figure 22-16 Maintenance of blood glucose levels by glucagon and insulin. When blood glucose levels are low, the pancreas secretes glucagon, which increases endogenous blood glucose levels through glycogenolysis. After a meal, when exogenous blood glucose levels are high, insulin is released to trigger glucose uptake into insulin-dependent muscle and adipose tissues as well as to promote glycogenesis. *Source:* Röder PV, Wu B, Liu Y, Han W. Pancreatic regulation of glucose homeostasis. *Exp Mol Med*. 2016;48(3):e219. Reproduced with permission.

Table 22-18 Regulation of glucagon.

↑ **Glucagon** secretion of glucagon is **stimulated by:**	• **Hypoglycemia** • Epinephrine • Arginine • Alanine (muscle-derived pyruvate/glutamate transamination • Acetylcholine • Cholecystokinin
↓ **Glucagon** secretion of glucagon is **inhibited** by:	• **Insulin (via GABA)** • Somatostatin • PPARγ/retinoid X receptor heterodimer • Increased free fatty acids and keto acids into the blood • Increased urea

but this control can be overridden during hypoglycemia. Both insulin and amylin are regulated by similar factors since they share a common regulatory promoter motif, with amylin being degraded in part by insulin-degrading enzymes and by peptidases in the kidney. A synthetic analogue of human amylin, pramlintide (Symlin®, AstraZeneca, Wilmington, DE, USA), is used in both T1DM and T2DM. Both insulin and pramlintide are injected separately, before a meal, to synergistically control the post-prandial glucose levels.[144]

Pathophysiology of Diabetes Mellitus

The pathophysiology of DM is mediated by alterations of carbohydrate metabolism and insulin action. After a meal, breakdown of carbohydrates leads to hyperglycemia, an elevation in blood glucose levels. Hyperglycemia stimulates insulin secretion from pancreatic beta cells because insulin is critical for glucose uptake by most cells (except in the brain). Insulin binds to specific cellular receptors and facilitates entry of glucose into the cell, which then uses the glucose for energy. The end result is a reduced blood glucose level and ultimately decreased insulin secretion. If insulin production and secretion are altered by disease, glucose entry into cells will be inhibited, resulting in sustained hyperglycemia.

Hyperglycemia can also ensue if insulin cannot function effectively, termed "insulin resistance." Following meals, the amount of glucose available often exceeds cellular demand for glucose. The excess glucose is stored in the liver in the form of glycogen, which serves as a ready reservoir of glucose for future use. When energy is required, glycogen stores in the liver are converted into glucose via glycogenolysis, elevating blood glucose levels and providing the needed cellular energy source. The liver also produces glucose from fat (fatty acids) and proteins (amino acids) through the process of gluconeogenesis. Glycogenolysis and gluconeogenesis

both serve to increase blood glucose levels. Thus, glycemia is controlled by a complex interaction between the gastrointestinal tract, the pancreas, and the liver. Insulin is the only hormone that lowers blood glucose levels. Counter-regulatory hormones such as glucagon, catecholamines, GH, thyroid hormone, and glucocorticoids all act to increase blood glucose levels, in addition to their other effects.

Type 1 Diabetes Mellitus

T1DM is characterized by idiopathic autoimmune destruction of pancreatic beta cells, usually leading to an absolute insulin deficiency (Tables 22-18 and 22-19).[4] It constitutes 5–10% of all DM cases. T1DM typically occurs before the age of 25 years in 95% of affected persons, but can occur at any age. It affects both sexes equally, and is more prevalent in Caucasians. The risk of developing T1DM is increased by a family history of T1DM, having gluten enteropathy (celiac disease), or other endocrine diseases. There are two distinct subclasses:

- *Immune-mediated form of T1DM*. This has a slow onset, with a subclinical prodromal period, characterized by cellular-mediated autoimmune destruction of the insulin-producing beta cell in the pancreatic islets. This may be triggered by a viral infection, but it is also associated with other autoimmune disorders, such as Hashimoto's thyroiditis, Addison's disease, vitiligo, or pernicious anemia.
- *Idiopathic T1DM*. This is acute in onset, and the cause of beta cell destruction is still unclear. It is prevalent among people of African or Asian origin and has a strong pattern of familial inheritance.[145]

Since the pancreas no longer produces insulin, a T1DM patient is completely dependent on exogenously administered insulin for survival. People with T1DM are highly susceptible to diabetic ketoacidosis. Although glucose is present, it is trapped in the circulation, but without insulin the cells are unable to take up the glucose. To meet cellular energy needs, fat is broken down through lipolysis, releasing glycerol and free fatty acids. Glycerol is converted to glucose for use by the cells. Fatty acids are converted to ketones, with an increase in the ketone levels in body fluids, which thus become increasingly alkaline (increased pH). Ketones are excreted in the urine, accompanied by large amounts of water. This accumulation of ketones in body fluids, increased pH, electrolyte loss, and dehydration from excessive urination, in addition to alterations in the bicarbonate buffering system, result in diabetic ketoacidosis. Untreated diabetic ketoacidosis can result in coma or even death. Many patients with T1DM are initially diagnosed following an episode of diabetic ketoacidosis.[146]

Table 22-19 American diabetes association diagnosis and classification of diabetes mellitus (DM).

1 Type 1 (Type 1 DM)	Formerly termed "juvenile diabetes" or "insulin-dependent diabetes"
2 Type 2 (Type 2 DM)	Formerly termed "adult-onset diabetes" or "non-insulin-dependent diabetes"
3 "Other"	A group of other types of DM caused by specific genetic defects of beta cell function or insulin action, diseases of the pancreas, or drugs or chemicals
4 Gestational diabetes	

Note: Arabic numbers are used instead of Roman numerals, thereby eliminating the confusion of type II, for example, as the number 11.

Type 2 Diabetes Mellitus

T2DM is the most common type of DM, constituting 90–95% of DM cases (Tables 22-18 and 22-19). It is characterized by insulin resistance in the peripheral tissues and/or defective insulin secretion by the pancreatic beta cells.[147] The etiology of T2DM is multifactorial, including genetic predilection, advancing age, obesity, and lack of exercise (Table 22-20).[10] Most T2DM patients are overweight, and most are diagnosed as adults.

Table 22-20 Risk factors for type 2 diabetes mellitus.

Diabetes-Related Risk Factors
Previously identified with: • impaired fasting glucose; or • impaired glucose tolerance; or • HbA1c of 5.7–6.4%
History of gestational diabetes or delivery of a baby >4 kg (9 lb)
Cardiovascular Risk Factors
History of cardiovascular disease
Hypertension (blood pressure ≥140/90 mmHg)
Dyslipidemia • high-density lipoprotein cholesterol level <35 mg/dL (0.90 mmol/L); and/or • triglyceride level >250 mg/dL (2.82 mmol/L)
Conditions/Diseases Associated with Development of Diabetes
Polycystic ovary syndrome
Acanthosis nigricans
Family History/Lifestyle Risk Factors
Family history of diabetes (i.e., parent or sibling with type 2 diabetes)
Race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
Obesity (body mass index [BMI] ≥25 kg/m^2)
Physical inactivity

The underlying pathophysiologic defect in T2DM does not involve autoimmune beta cell destruction, and is characterized by the following three features:

- Peripheral resistance to insulin, especially by the muscle cells.
- Increased production of glucose by the liver.
- Defective insulin secretion by the pancreatic beta cells.[5]

Increased tissue resistance to insulin generally occurs first, followed by impaired insulin secretion. The pancreas produces insulin, yet insulin resistance prevents its proper use at the cellular level. Glucose cannot enter target cells and accumulates in the bloodstream, resulting in hyperglycemia. The high blood glucose levels often stimulate an increase in insulin production by the pancreas; thus, people with T2DM often have excessive insulin production (hyperinsulinemia), but then, over several years, this drops to below normal levels.

In addition to hyperglycemia, patients with T2DM often have a group of disorders called "metabolic syndrome" comprising hyperglycemia, hypertension, dyslipidemia, atherosclerosis, and central or abdominal obesity (Table 22-20).[148] Obesity contributes greatly to insulin resistance and may explain the dramatic increase in the incidence of T2DM in the United States and worldwide in the past 10–20 years. Other risk factors include advancing age, high caloric intake, sedentary lifestyle, and low birth weight. People with impaired glucose tolerance, impaired fasting glucose, and gestational DM have a high risk of developing T2DM later in life, with these conditions being considered the preclinical stages of T2DM.

T2DM has a slow onset and may remain undiagnosed for years, given that some 50% of affected people are unaware of their disease. By the time many T2DM patients are diagnosed, diabetic complications and the consequent morbidity are already established. T2DM patients do not require exogenous insulin for survival since they still produce insulin. However, insulin is often an integral part of medical management for T2DM. Unlike patients with T1DM, those with T2DM are generally resistant to diabetic ketoacidosis, because their pancreatic insulin production is often sufficient to prevent ketone formation, although severe physiologic stress can still induce diabetic ketoacidosis in those with T2DM. Long periods of severe hyperglycemia can result in hyperosmolar nonketotic acidosis. This occurs when hyperglycemia results in the urinary excretion of large amounts of glucose, with attendant water loss. If this fluid is not replaced, dehydration can result in electrolyte imbalance and acidosis.

Gestational DM includes the development of T1DM or the discovery of undiagnosed asymptomatic T2DM during pregnancy.[8] Approximately 2–5% of pregnant women in the United States develop a mild degree of fasting hyperglycemia or glucose intolerance during the third trimester, which significantly increases perinatal maternal morbidity and mortality. Some 30–50% of women with gestational DM will develop T2DM within 10 years.

Diagnosis and Monitoring

The diagnosis of DM is based on specific laboratory findings, as well as the presence of clinical signs and symptoms. Diagnostic guidelines include testing of the fasting and nonfasting glucose levels. Diagnosis is not made until the patient has exceeded threshold glucose levels on two separate occasions. The classic signs of DM vary in number and order, but are typically described as (1) polyuria (frequent urination); (2) polydipsia (increased thirst); (3) polyphagia (increased hunger); (4) weight loss; and (5) either disturbed (blurry) vision or peripheral neuropathy.

Glycosylated Hemoglobin Assay

The glycosylated hemoglobin assay (HbA1c) allows the determination of blood glucose status over the 30–90 days prior to collection of the blood sample. It has now been officially recommended as one of the tests for the definitive diagnosis of DM, for screening of individual patients suspected to have DM, and for population screening. As glucose circulates in the bloodstream, it becomes attached to a portion of the hemoglobin molecule on red blood cells (like barnacles on a ship). The higher the plasma glucose levels are over time, the greater the percentage of hemoglobin that becomes glycosylated. The American Diabetes Association recommends that individuals with DM attempt to achieve a target HbA1c value of less than 7%. An HbA1c value of more than 8% suggests that a change in patient management may be needed to improve glycemic control.[4] The HbA1c can provide false-positive and -negative values in rare situations, such as patients with severe iron deficiency and those with any form of hemoglobinopathy, for example sickle cell disease.

Glucometers

The development of small, accurate, handheld glucometers has allowed the diabetic individual to take much greater control of their disease. Glucometers use a small drop of capillary blood from a finger-stick sample to assess glucose levels within seconds.[149]

Screening

The American Diabetes Association recommends screening all individuals >45 years every 3 years, and screening individuals at an earlier age if they are overweight (body mass index [BMI] >25 kg/m^2) and have one additional risk factor

for diabetes, as listed in Table 22-19. Dental healthcare providers are well placed to undertake screening of their patients for diabetes.[150–152]

Management

The primary treatment goals for DM are to achieve blood glucose levels as close to normal as possible and to prevent diabetic complications.[13] Secondary goals are to maintain normal growth and development, normal body weight, the avoidance of sustained hyperglycemia or symptomatic hypoglycemia, and the prevention of diabetic ketoacidosis and nonketotic acidosis. The other major aim is the prevention and management of the long-term complications of diabetes. Diet, exercise, weight control, and medications (Table 22-21) are the mainstays of diabetic care. Weight reduction and exercise improve tissue sensitivity to insulin and allow its proper use by target tissues.

Medications

Drugs used to treat DM lower glucose levels in the blood. With the exceptions of insulin, exenatide, liraglutide, and pramlintide, all are administered orally and are therefore also called oral hypoglycemic agents or oral antihyperglycemic *agents* (see Table 22-22).[153,154]

Gastric Banding and Gastric Bypass Surgery

These surgical treatments are indicated for patients with severe, morbid obesity who are unresponsive to 6 months' intensive attempts at dieting and graded exercise. FDA-recommended BMI thresholds for surgery range from 30–40 kg/m^2, with one or more obesity-related medical conditions: hypertension, heart disease, DM, or sleep apnea. The surgical risks and postoperative complications are frequent and potentially severe. Also, long-term intensive specialist care and follow-up are needed, including psychologic support and nutritional supplements (subsequent to bowel resection procedures). About one-third of DM patients have complete resolution of their disease, becoming medication free.[155,156] However, DM can still recur.

Insulin

All patients with T1DM use exogenous insulin, as do many with T2DM. Insulin is given via subcutaneous injection. Insulin infusion pumps deliver insulin through a subcutaneous catheter. Ideally, the use of exogenous insulin provides an insulin profile similar to that seen in a nondiabetic individual, with a continuous basal level of insulin availability augmented by increased availability following each meal (see Tables 22-21, 22-22, and 22-23).

Human insulin is only absorbed slowly, reaching a peak 60–90 minutes after subcutaneous injection, and its action tends to persist after meals, predisposing to hypoglycemia. Rapid-acting insulins (insulin lispro, insulin aspart, and insulin glulisine) enter the circulation more rapidly than human soluble insulin, but also disappear more rapidly and are of limited effectiveness.[157]

The action of human insulin can be prolonged by the addition of zinc or by the addition of protamine. The most widely used form is neutral protamine hagedorn (NPH or isophane insulin), which is a suspension of crystalline zinc insulin combined with protamine; this has an intermediate duration of action that is longer than that of regular insulin, but shorter than ultralente, glargine, or detemir. NPH has the advantage that it can be premixed with soluble insulin to form stable mixtures (biphasic insulins), of which the combination of 30% more readily soluble absorbable insulin with 70% NPH is most widely used. The intermediate-acting insulins (lente and NPH) take several hours after injection to begin having an effect. Peak activity varies among individuals and sites of injection, but generally occurs 4–10 hours after injection.

Long-acting insulins include insulin glargine. This form of insulin is soluble in the vial as a slightly acidic (pH 4) solution, but precipitates on subcutaneous injection, which prolongs its duration of action. Ultralente insulin is the longest-acting insulin. Commonly called "peakless" insulin, ultralente has a very slow onset of action, minimal peak activity, and a long duration of action. It is usually taken to mimic the basal metabolic rate of insulin secreted from a normally functioning pancreas (see Table 22-22).

Insulin Complications

The most common complication of insulin therapy is hypoglycemia, a potentially life-threatening emergency.[10] Intensified treatment of DM to achieve a tightly regulated blood sugar level increases the risk of hypoglycemia. One-third of severe hypoglycemic episodes result in seizure or loss of consciousness and 36% of episodes occur with no warning symptoms for the diabetic patient. The phenomenon known as "hypoglycemia unawareness" is more common in diabetic patients with good glycemic control than in those with poor control. Signs and symptoms of hypoglycemia are most common when blood glucose levels fall to <60 mg/dL, but they may occur at higher levels in diabetic patients with chronic poor metabolic control.[13] In people with hypoglycemia unawareness, glucose levels can fall to 40 mg/dL or lower before an individual feels or reports being unwell.[158]

Pancreas or Beta-Islet Cell Transplantation

Transplantation of the whole pancreas or just the pancreatic islet cells is an option for T1DM, particularly for patients with severe or poorly controlled disease.[159]

Table 22-21 Drug therapies used for diabetes mellitus.

Oral Agents					
Insulin Sensitizers					
Class	**Actions**	**Generic Name**	**Trade Name(s)[a]**	**Advantages**	**Disadvantages/ Warnings**
Biguanides	↓ Hepatic glucose production ↓ Intestinal absorption of glucose Improves insulin sensitivity by increasing peripheral glucose uptake and utilization	Metformin	Diabex Fortamet Glucophage Glumetza Riomet	Weight neutral No hypoglycemia	Lactic acidosis with metformin: risk increases with degree of renal impairment, patient's age, unstable/ acute congestive heart failure
Thiazolidinediones ("glitazones")	↑ Tissue sensitivity to insulin ↓ Hepatic gluconeogenesis ↓ Glucose use ↓ Blood glucose levels.	Rosiglitazone Pioglitazone	Avandia Actos	Lower insulin requirements No hypoglycemia	May increase risk of congestive heart failure and myocardial infarction
Insulin Secretagogues (Increase Insulin Release)					
Sulfonylureas (1st generation)	↓ Lowers blood glucose acutely	Tolazamide Tolbutamide	Tolazamide Orinase	?	Significant adverse side effects (relative to 2nd-generation sulfonylureas)
Sulfonylureas (2nd generation)	↑ Insulin by stimulating its release from pancreas	Gliclazide[b] Glimepiride Glipizide Glyburide	Diamicron[b] Amaryl Glucotrol DiaBeta Glynase	More potent, but fewer side effects or drug interactions	Hypoglycemia Increased risk of cardiovascular mortality
Nonsulfonylurea Insulin Secretagogues					
Meglitinides	↓ Lowers blood glucose ↑ Insulin by stimulating its release from pancreas	Nateglinide Repaglinide	Starlix Prandin	Acts similar to sulfonylureas but much shorter half-life	Hypoglycemia
Alpha-Glucosidase Inhibitors (Have No Effect on Insulin)					
α-Glucosidase Inhibitors	↓ Digestion and ingestion of glucose (in the form of starch) from the gastrointestinal tract	Acarbose Miglitol	Precose Glyset	Reduce postprandial hyperglycemia	Flatulence Inhibits hydrolysis of sucrose to glucose and fructose; use oral glucose (dextrose) instead of sucrose in treatment of mild–moderate hypoglycemia

(*Continued*)

Table 22-21 (Continued)

Oral Agents					
Insulin Sensitizers					
Class	**Actions**	**Generic Name**	**Trade Name(s)[a]**	**Advantages**	**Disadvantages/ Warnings**
Glycosuric Agents					
Sodium/glucose cotransporter 2 (SGLT2) Inhibitors	↓ Reabsorption of renally filtered glucose ↓ Lowers renal threshold for glucose, thereby increases urinary glucose excretion ↓ Glucose blood levels	Canagliflozin Dapagliflozin[b] Empagliflozin	Invokana Forxiga[b] Jardiance	Weight reduction Reduced blood pressure	Hypotension Hyperkalemia Genital mycotic infections, urinary tract infection, increased urination
Dipeptidyl Peptidase-4 Inhibitors					
Dipeptidyl peptidase-4 inhibitors	↓ Enzymic inactivation of incretin hormones, thereby increasing serum concentrations ↓ Fasting and postprandial glucose blood levels	Alogliptin Linagliptin Saxagliptin Sitagliptin Vildagliptin[b]	Nesina Tradjenta Onglyza Januvia Galvus[b]	No hypoglycemia	Angioedema
Parenteral Agents					
Insulin					
Short-acting Long-acting Combination (short- and long-acting)	↑ Glucose utilization (and absorption) ↓ Hepatic gluconeogenesis	Various (see Table 22-11)		Known and predictable safety profile	Parenteral: injection needed Weight gain (increases hunger) Hypoglycemia
Incretin Mimetics					
Gastric inhibitory peptide (GLP-1) agonists	↑ Insulin ↓ Glucagon	Exenatide Liraglutide	Bydureon (XR) Byetta Victoza	Slow gastric emptying and so increase satiety, leading to weight loss	Injection Hypoglycemia Nausea Pancreatitis
Amylin analogues	Modulation of gastric emptying ↓ Postprandial rise in plasma glucagon ↑ Satiety	Pramlintide	Symlin	Satiety ↓ Caloric intake → Potential weight loss Regulates food intake	Parenteral: injection needed Increased risk of insulin-induced severe hypoglycemia (especially in patients with type 1 diabetes mellitus)

↓, decreases; ↑, increases; →, leads to; ?, uncertain; XR, extended release

[a] Table entry refers to the single agent. Oral antidiabetic agents are often prescribed and supplied in combination with other antidiabetic agents.

[b] Not marketed in the United States.

Source: Data from MIMS Australia (http://www.mims.com.au/index.php/about-mims/mims-australia) and Rx List (https://www.rxlist.com/script/main/hp.asp).

Table 22-22 Types of insulin.

Type	Class	Onset of Activity (h)	Peak Activity (h)	Duration of Activity (h)
Lispro	Rapid-acting	0.25	0.5–1.5	<5
Insulin aspart (Novorapid)	Rapid-acting	0.25	0.67–1.5	3–5
Insulin glulisine (Apidra)	Rapid-acting	0.2	0.67–1.5	3–5
Regular	Short-acting	0.5–1.0	2–3	4–12
Lente	Intermediate-acting	3–4	4–12	16–20
Neutral protamine hagedorn	Intermediate-acting	2–4	4–10	14–18
Insulin detemir	Long-acting	Onset 2 h	No peak	6–24
Insulin glargine	Long-acting	Onset 2 h	No peak	20 to >24
Ultralente	Long-acting	6–10	12–16	20–30

Table 22-23 Common insulin regimens.

Insulin(s) Description	Frequency of Injection	Timing of Injection	Characteristics
intermediate-acting	Single (1×) daily	Morning early	• Peak insulin activity at midday • Can provide enough insulin for midday meal only • Hyperglycemia common upon rising, following breakfast and dinner
Mixture of intermediate-acting and regular or rapid-acting	Single (1×) daily	Morning early	• Peak insulin activity at both mid-morning (from regular or lispro insulin) and midday (from intermediate-acting insulin) can provide enough insulin for breakfast and midday meals Hyperglycemia common on rising and late afternoon to next morning
Intermediate-acting	Twice (2×) daily	Prior to breakfast Prior to dinner	• Peak insulin activity at both midday (from morning injection) and evening (from dinner injection) • Can provide enough insulin for lunch and sometimes dinner to prevent early-morning high blood glucose levels • Hyperglycemia common after breakfast and shortly after dinner
Mixture of intermediate-acting and regular or rapid-acting	Twice (2×) daily	Prior to breakfast Prior to dinner	• Peak insulin activity after breakfast (from morning regular or lispro insulin), after lunch (from morning intermediate-acting insulin), after dinner (from dinnertime regular or lispro insulin), and late evening or early morning (from dinnertime intermediate-acting insulin) • Can provide enough insulin for all meals • Prevents early-morning high blood glucose levels
Regular or rapid-acting and one injection of intermediate-acting	Three (3×) daily	Prior to each main meal	• Peak insulin activity after breakfast, lunch, and dinner (from regular or lispro insulin before each meal) and late evening or early morning (from dinnertime intermediate-acting insulin) • Can provide enough insulin for all meals • Prevents early-morning high blood glucose levels
	Single (1× daily)	Bedtime	• Provides better glycemic control than once- or twice-daily injection regimens
Ultralente and regular or rapid-acting	Once (morning)	Morning	• Peak insulin activity after breakfast, lunch, and dinner (from regular or lispro insulin before each meal), insulin activity in late evening or early morning (from morning Ultralente insulin)
	Three (3×) daily	Prior to each main meal	• Can provide enough insulin for all meals • Prevents early-morning high blood glucose levels • Provides better glycemic control than once- or twice-daily injection regimens
Infusion* regular or rapid-acting	Continuous with bolus (before meals)	See note	• Provides on-demand insulin with meals • Basal metabolic rate most closely mimics normal pancreatic function • Often (not always) provides best glycemic control

* Rate set to provide continuous low dose with bolus programmed to be given prior to each meal.

Complications of Diabetes Mellitus

Life expectancy is considerably reduced in patients with DM (Table 22-24). The major causes of death are cardiovascular complications, renal failure, and infection(s).[160,161] The pathophysiology is related to (1) nonenzymatic glycosylation of proteins such as hemoglobin, collagen, and tubulin in peripheral nerves, thus impairing their function and also leading to an accumulation of advanced glycosylated end-products, causing injury and inflammation;[162] and (2) disruption of the polyol pathway[163] of the vascular endothelium, with the metabolism of glucose being increased by intracellular aldose reductase, which leads to the accumulation of sorbitol and fructose that causes changes in vascular permeability, cell proliferation, and capillary structure.

Table 22-24 Complications of diabetes mellitus.

System/Organ	Presentation
Cardiovascular system	Macrovascular disease (accelerated atherosclerosis) leading to peripheral vascular disease, coronary artery disease and cerebrovascular disease, ischemic ulcers, andgangrenous feet
Nervous system	Sensory: peripheral neuropathy, cranial neuropathy affecting cranial nerves III, IV, VI, VII Autonomic: gastroparesis; changes in cardiac rate, rhythm, and dysfunction; postural hypotension; gastrointestinal neuropathy; urinary bladder atony; impotence
Kidney	Nephropathy, renal failure
Skin and oral mucosa Periodontium	Unusual infections, delayed wound healing Gingivitis and periodontal diseases
Eyes	Retinopathy, cataracts, blindness

Macrovascular Complications

Diabetes is a risk factor for the development of atherosclerosis (Table 22-25). Consequently, myocardial infarction is 3–5 times more likely for both diabetic men and women. Similarly, stroke is two times higher and foot amputation for gangrene is 50 times more likely to occur.

Microvascular Complications

Small blood vessels throughout the body are affected, but the disease process is of particular concern in three sites: retina, renal glomerulus, and nerves (specifically the nerve sheath), the latter resulting in a variety of sensory and autonomic neuropathies.

Infectious Complications

Infections in diabetics tend to be more frequent and generally more severe (Table 22-26), due to abnormalities of cell-mediated immunity and impaired polymorphonuclear leucocytes (neutrophil) function. Neutrophil chemotaxis and phagocytosis are diminished, because at high blood

Table 22-25 Macrovascular complications of diabetes and their management.

Risk Factor	Aim	Treatment/Intervention
Duration of diabetes mellitus	Maintenance of optimal glycemic control	Frequent monitoring, by patient and health professionals
Hypertension	Aggressive maintenance of target blood pressure	Usually requires a combination of antihypertensive agents: angiotensin-converting enzyme (ACE) inhibitors and/or angiotensin II receptor antagonists
Myocardial infarction/stroke		Aspirin (low dose): reduces macrovascular risk, but is associated with complications from bleeding
Proteinuria (including microalbuminuria)	Regular urinary analysis	Urine to be checked regularly (at least annually) for proteinuria Screening of younger patients for microalbuminuria
Dyslipidemia/ hyperlipidemia	Aggressive control of hypercholesterolemia	Statins: there is no "safe" cut-off for serum cholesterol, so the lowest achievable level seems best practice
Other factors (as per the general population): Aging Smoking Excessive alcohol intake Poor diet	Avoidable/modifiable	Consistent efforts should always be made to address modifiable risk factors

Table 22-26 Infectious complications in diabetic patients.

Site/Organ	Infectious Organism(s)	Clinical Entity
Skin	*Staphylococcal* spp.	Boils Abscesses Carbuncles
Mucosa	*Candida* spp.	Mucocutaneous candidiasis Vulvo-vaginal candidiasis
Oral cavity	Mixed bacterial infection	Periodontal disease
Bone	*Staphylococcal* spp.	Spontaneous spinal osteomyelitis
Lung	*Staphylococcal* spp. *Pneumococcus* spp. Gram-negative bacteria	Pneumonia
	Tuberculosis	Pulmonary tuberculosis
Gastrointestinal tract	Mixed bacterial infection	Rectal and ischiorectal abscesses
Urinary tract	Mixed bacterial infection	Urinary tract infections (in women) Pyelonephritis Perinephric abscess

glucose concentrations neutrophil superoxide generation is impaired, and there is reduced tissue vascularity (reduced microcirculation/number of vessels and capillaries in the tissues). Reduced tissue vascularity results in hypoxia and ischemia that limit the access of neutrophils and any antibiotic given to the patient to sites of infection. Hyperglycemia also aids in the colonization and growth of *Candida* and other fungi, and of select bacterial species. Conversely, all types of infections may lead to impaired glycemic control and are a common cause of ketoacidosis. Insulin-treated patients need to increase their insulin dose(s) by up to 25% when infection occurs, and non-insulin-dependent diabetics may need insulin to be instituted during the course of the infection.[164] Apart from increased frequency and severity of common infections, there are district rare infections of diabetic populations: malignant, invasive otitis externa, usually secondary to *Pseudomonas aeruginosa*, which can lead to osteomyelitis and even meningitis; emphysematous (gas-forming) bacterial infections of the gall bladder and urinary tract; and rhinocerebral mucormyositis of the sinuses.[165]

Stomatognathic Manifestations and Complications of Diabetes Mellitus

Dentists also must be prepared to provide, sometimes highly invasive, surgical treatment for patients with DM, which may include the use of general anesthesia (Table 22-27). Good oral health, especially the prevention and treatment of infections, such as the various forms of candidiasis, periodontal disease, and odontogenic-related soft tissue infections and cellulitis, is essential for the maintenance of glycemic control, and the diabetic patient's overall wellbeing and health.[166]

Medical History and Review of Physiologic Systems

The focus of a thorough medical history and review of systems is to determine both the severity and stability of the medical condition(s). Stability of DM is the more critical concern. It can be readily assessed by reviewing the patient's ongoing glycemic control, such as their self-assessment of fasting and nonfasting blood glucose levels using a home glucometer, or arranging testing of HbA1c, which serves as a useful assessment of glycemic control for the last three months. Other important clues to glycemic control are the number and severity of the known complications of DM. These include the state of their cardiovascular health, which is critical to safe dental treatment, the frequency of hypoglycemic episodes, or the length of time since the patient's last hypoglycemic episode. For T2DM patients, the number of medications they use, recent adjustments in the dose or frequency of their medications, and whether they require insulin as part of their management regimen are also highly informative in determining the level of their glycemic control. A favorable outcome of recent dental extractions and surgery within the past 3–6 months is also indicative of a favorable outcome for any dental surgery needed in the immediate future.

The most likely and serious complication is inadvertent hypoglycemia, in a patient taking their normal medication, especially insulin, but failing to eat, either because of a dental problem associated with discomfort and pain, or the

Table 22-27 Oral and dental findings with diabetes mellitus.

Clinical Finding (Sign)	Description	Etiology/Pathophysiology
Extraoral Findings		
Sialosis	Bilateral diffuse swelling of the parotid glands, in the absence of any other identifiable cause of bilateral parotid sialoadenopathy	Autonomic neuropathy
Angular cheilitis	Unilateral, but typically bilateral moist fissuring of the corners of the lips/mouth (commissures)	Infection (secondary to impaired immunity): *Candidal* spp. with coinfection from staphylococcal bacterial species resident on the perioral skin.
Intraoral Findings		
Hyposalivation	Clinical evident decrease in total volume of unstimulated and stimulated salivary flow Smooth surface dental caries Atrophy and desiccation of mucosal surfaces Atrophy of papillae of dorsal tongue	Autonomic neuropathy Dehydration secondary to polyuria
Candidiasis		Infection (secondary to impaired immunity) with contributory factors including hyposalivation, and increased presence in saliva of glucose
Oropharyngeal candidiasis	White, adherent, small plaques that on removal leave a red, superficially bleeding area scattered over the oral and oropharyngeal mucosa	
Atrophic candidiasis	Erythematous, atrophic oral mucosa, particularly of the hard palate	
Denture stomatitis	Markedly erythematous, atrophic oral mucosa of the denture-fitting surfaces of the oral mucosa (particularly the palate)	
Medium rhomboid glossitis	Erythematous, well-demarcated, somewhat rhomboid-shaped area of mucosa of the central dorsal surface of the tongue	
Periodontal disease(s)	Localized or generalized periodontal changes, with gingival erythema, presence of increased tooth mobility, and bleeding on periodontal probing, with associated alveolar bone loss, evident radiographically	Infection secondary to impaired immunity, due to accumulation of dental plaque and impaired neutrophil response (deficient chemotaxis and bacterial killing)
Poor oral hygiene	Bacterial plaque deposits and/or calculus readily evident on tooth surfaces, with gingivitis and easy bleeding of gingiva	Impaired manual dexterity, secondary to sensory and autonomic neuropathy affecting hands/fingers
Oral lichen planus/ lichenoid mucositis	Striae: fine white-gray lines on erythematous background, typically bilateral, involving buccal or latero-ventral surfaces of tongue, with similar-colored discrete plaques and/or mucosal ulceration and/or desquamative gingivitis	Lichenoid drug reaction to oral hypoglycemic agents (e.g., chlorpropamide)

mistaken belief in the need to fast prior to a dental procedure. Odontogenic-related infections (periapical periodontitis) that result in either in a collection in the adjacent soft tissues or cellulitis can trigger ketoacidosis. Therefore, a simple precaution before undertaking highly invasive dental surgical procedures is to check the patient's blood glucose level by means of an inexpensive, compact, point-of-care glucometer. A hypoglycemic patient can be provided with replacement sugar. For a conscious patient, this can be in the form of a glucose drink of 150 mL carbonated lemonade, two teaspoons of table sugar (sucrose), or preferably glucose (dextrose) in water. The clinician should check for patient recovery and recheck their blood glucose level.

For patients with a deteriorating level of consciousness, this represents an evolving medical emergency, requiring the prompt institution of first aid, and if necessary intramuscular administration of 1 mg glucagon (see later).

Oral Candidiasis

When DM patients present with candidiasis in any of its clinical forms, it is indicative of impaired glycemic control. Therefore, patients' random blood glucose and hemoglobin HbA1c should be checked. The treatment of oral fungal infections in DM patients is similar to that for standard patients, with the added consideration that topical antifungal medications need to be sugar free.

Periodontal Disease

Periodontal disease has been referred to as the sixth sign[167] or complication of DM, and the longer the duration of DM, the greater the likelihood of developing severe periodontal disease.[168,169] Severe periodontitis has also been suggested to be a risk factor for poor glycemic control.[170,171] Since glycemic control is connected to periodontal disease and progressive alveolar bone loss,[172] periodontal treatment must be in parallel with DM treatment.[173–177] There is firm evidence of improvement in glycemic control in diabetic patients that receive treatment of their periodontal disease. There is a modest, but significant, improvement in glycemic control, reflected by a 0.4% reduction in glycated hemoglobin levels.[178] Importantly, this modest benefit in the glycated hemoglobin level, as a result of periodontal therapy, when combined with other interventions, such as diet modification and exercise, may be sufficient to prevent or at least limit the number of medications required for good diabetic control, thereby limiting the cost to the patient and/or the healthcare system.[179,180]

Edentulism

Rates of tooth loss in patients with DM are not only higher compared with nondiabetic patients, but also more rapid, resulting in higher rates of edentulism at a younger age.[181] The main causes of tooth loss are predominantly due to dental caries and periodontal disease. It appears that diabetes per se does not directly contribute to tooth loss, but the combined effects of hyposalivation and peripheral neuropathy that affect manual dexterity are significant contributing factors, because they promote the formation, persistence, and growth of dental plaque. It is also important to note that the same causal lifestyle factors for T2DM—poor levels of health education, personal neglect, poor lifestyle choices, reflected in poor dietary choices—are also contributing factors to dental disease, with poorer levels of oral hygiene seen in this same group of patients.[182]

Dental Implants

DM is not a contraindication for dental implants. Although there is concern that implant survival may be reduced, a long-term cohort study demonstrated that smoking was independently a more significant and adverse factor for implant survival than DM. The study also showed that excellent frequent and regular implant maintenance was a significant factor to ensure and improve long-term implant survival.[183] As in all patients irrespective of diabetic status, appropriate patient selection and eradication of comorbidities such as poor oral hygiene, cigarette smoking, and periodontitis are critical to implant success. For patients with DM, one study demonstrated that stabilization of glycemic control HbA1c at around 7% and prevention of infection increased the success of dental implants to a satisfactory rate of 85–95%. The use of antibiotics at the time of implant placement for patients with DM is still debatable, as there is limited evidence that it may provide some benefit.

Dental Treatment Planning Considerations

Appointment Scheduling

Generally, the best time for dental treatment is either before or after periods of peak insulin activity. This reduces the risk of perioperative hypoglycemic reactions, which occur most often during peak insulin activity. The greatest risk would occur in a patient who has taken the usual amount of insulin or oral hypoglycemic agent but has not eaten prior to dental treatment. Patients with poor long-term glycemic control and patients with a history of severe hypoglycemic episodes are at greater risk of future hypoglycemia. Often it may not be possible to plan dental treatment in a way that will avoid peak insulin activity. This is particularly true for patients who take frequent insulin injections; these patients have greater risks of developing perioperative hypoglycemia. Pretreatment blood glucose level can be measured with a glucometer, and there should be a readily available source of carbohydrates in the dental office.[173]

Treatment Aims

For patients with sub-optimally controlled DM, treatment should be focused on addressing any active infection, and likely sources or sites of infection in the immediate future, such as periodontally compromised teeth with questionable prognosis. Odontogenic infections should also be aggressively addressed, by extracting the offending tooth or with root canal therapy (if appropriate), with an emphasis on excellent postoperative analgesia by using long-acting local anesthetics and opiate-containing analgesics. This may require aggressive surgical management with drainage of collections in the adjacent soft tissues, and antibiotic coverage. Hospital admission to stabilize the patient's blood glucose levels, and manage infection by surgery and intravenous antibiotics, may be merited. Extensive, elective dental treatment should be delayed until the patient's diabetes is better controlled.

For diabetic patients, it is important to ensure that the patient is able to eat and/or drink to replenish their glucose levels. Hypoglycemia can occur as a consequence of fasting, and happens more easily and more rapidly, so is a more critical concern than hyperglycemia. This can be best addressed by rechecking the patient's postoperative blood glucose level, providing supplementary glucose in the form of a drink (lemonade, orange juice), and ensuring that the patient travels home by private transport and that someone is at home to care for them on discharge from the clinic.

As to the specifics of patient positioning in the dental chair, patients with long-standing DM may have developed some degree of autonomic neuropathy with associated orthostatic hypotension. Thus it is vital to slowly and carefully raise the patient from the supine to the upright or standing position.

Drug Use and Adverse Drug Interactions

There are few significant drug interactions in DM (Table 22-28). The exception is metformin with radiographic iodine contrast, in which case temporary cessation of the metformin to allow time for the contrast to be administered and the imaging completed is recommended.

Table 22-28 Diabetic drugs—interactions with drugs relevant to dentistry/oral medicine.

Insulin Sensitizers

Class	Generic Name	Trade Name(s)[a]	Drug Interaction*		Comment
Biguanides	Metformin	Diabex Fortamet Glucophage Glumetza Riomet	Iodinated radiographic contrast	**S**	Recommendation is for temporary discontinuation of metformin
Insulin Secretagogues (Increase Insulin Release)					
Sulfonylureas (1st generation)	Tolazamide	Tolazamide	Hypoglycemic effects potentiated by NSAIDs and miconazole	?	
	Tolbutamide	Orinase			**
Sulfonylureas (2nd generation)	Gliclazide[b]	Diamicron[b]			
	Glimepiride	Amaryl	Hypoglycemic effects potentiated by NSAIDs, some azoles (miconazole, fluconazole)	?	**
	Glipizide	Glucotrol			
	Glyburide	DiaBeta Glynase			
Nonsulfonylurea Insulin Secretagogues					
Meglitinides	Nateglinide	Starlix	NSAIDs and CYP2C9 inhibitors: fluconazole, miconazole, may potentiate hypoglycemia	?	
	Repaglinide	Prandin	CYP3A4 and/or CYP2C8 inducers: carbamazepine, CYP3A4 inhibitors: erythromycin and OATP1B1 inhibitors: itraconazole, ketoconazole, clarithromycin	?	
Insulin					
Short-acting Long-acting Combination (short- and long-acting)	Various (see Table 22-14)		Epinephrine Corticosteroids	? S	
Incretin Mimetics					
Amylin analogues	Pramlintide	Symlin	Do not administer with agents that alter gastrointestinal motility (e.g., anticholinergic agents such as atropine) and pilocarpine (cholinergic agonists)	**S**	

[a] Table entry refers to the single agent. Oral antidiabetic agents are often supplied combined with other agents.
[b] Not marketed in the United States
* Corticosteroids all cause loss of glycemic control, but generally not mediated by adverse interaction with drugs used for the management of diabetes mellitus, except for insulin.
** Only isolated case reports of severe hypoglycemia with coadministration of miconazole.
CYP, cytochrome (superfamily of proteins found in hepatocytes and responsible for metabolism of organic substances); NSAID, nonsteroidal anti-inflammatory drugs; OATP, organic anion-transporting polypeptide, membrane transport proteins that mediate the transport of mainly organic anions across cell membranes; S, serious; ?, theoretical risk with no or limited case reports documenting adverse interaction.

Epinephrine (in Local Anesthetics)

Epinephrine is not contraindicated in diabetic patients per se, because it helps promote better dental anesthesia and significantly lowers the amounts of endogenous epinephrine released in response to pain and stress. However, in a patient with concomitant cardiovascular or renal disease, the level of epinephrine may need to be reduced to two or fewer carpules of local anesthetic containing 1:100,000 epinephrine. Two small-scale studies compared DM patients to controls and found no significant alteration in blood glucose levels after dental treatment, such as extractions, which required administration of local anesthetic with epinephrine.[184,185]

Corticosteroids

Topical and systemic corticosteroids have established value in a range of oral dermatoses; however; because of their physiologic actions rather than their drug interactions, dysregulation of glycemic control may ensue. Corticosteroids profoundly affect carbohydrate and lipid metabolism, designed to protect the glucose-dependent tissues (and their cells) such as the heart (cardiac myocytes) and brain (neurons) from starvation. Corticosteroids increase blood glucose levels by stimulating the liver to form glucose from amino acids and glycerol, and to store glucose as glycogen. In the periphery, corticosteroids increase protein breakdown and activate lipolysis. All these contribute to increased blood glucose levels that worsen glycemic control in patients with overt diabetes and precipitate the onset of hyperglycemia in susceptible patients, potentially leading to frank DM. Corticosteroids should be used with caution in collaboration with the patient's physician. If systemic corticosteroids are required, an adjustment of DM drugs may be necessary. Regular monitoring of glucose levels will be paramount to ensure good glycemic control.

Major Surgery, General Anesthesia, and Hospital Admission

Type I Diabetes Mellitus

Recommendations for those with T1DM undergoing general anesthesia and surgery:

- Long-acting and/or intermediate insulin should be stopped the day before surgery, with soluble insulin substituted.
- Diabetic patients should be first on the morning appointment list.
- Infuse glucose, insulin, and potassium during surgery. The insulin can be mixed into the glucose solution or administered separately by syringe pump. (The standard combination is 16 U of soluble insulin with 10 mmol potassium chloride in 500 mL 10% glucose, infused at 100 mL/h.) Any other intravenous fluids needed must be given through a separate intravenous line so as not to interrupt the glucose/insulin/potassium infusion.
- Postoperatively the infusion is maintained until the patient is able to eat.
- Glucose levels are checked every 2–4 hours and potassium levels are monitored and, if necessary, adjusted by provision of replacement insulin, dextrose, and/or potassium.

Type 2 Diabetes Mellitus

Patients with mild hyperglycemia (fasting blood glucose below 8 mmol/L [144 mg/dL]) can be treated as nondiabetics. For patients reliant on oral antidiabetic agents for management of their DM, they should stop medication two days before surgery. Moreover, these oral agents are of concern if the patient is fasting (in particular the risk of hypoglycemia with sulfonylurea agents). Those type 2 diabetics with poorly controlled diabetes can be managed with an insulin infusion or subcutaneous long-acting insulin plus preprandial, short-acting insulin.

Managing the Diabetic Emergency in the Dental Office

Hypoglycemia is a potentially life-threatening situation that must be recognized and treated expeditiously. Signs and symptoms include confusion, sweating, tremors, agitation, anxiety, dizziness, tingling or numbness, and tachycardia. Severe hypoglycemia may result in seizures or loss of consciousness. Prevention starts with the practitioner being familiar with the general medical risks for hypoglycemic events (Table 22-29) and assessing the patient's risk for developing hypoglycemia (Table 22-30). Every dental office that treats DM patients (see Table 22-31) should have readily available sources of oral carbohydrates (e.g., fruit juice, nondiet soda, hard candy). As soon as a patient

Table 22-29 General management considerations for the patient with diabetes.

Assess level and stability of glycemic control
Refer patients with signs and symptoms suggestive of undiagnosed or uncontrolled diabetes to physician for diagnosis and treatment
Obtain medical consultation if systemic complications are present
Use a glucometer to help avoid emergencies related to diabetes
Treat acute oral infections aggressively
Place patients on frequent recall visits to monitor and treat oral complications and maintain optimal oral hygiene and diet

Source: Adapted from Vernillo AT. Dental considerations for the treatment of patients with diabetes mellitus. *J Am Dent Assoc.* 2003;134:24S–33S.

Table 22-30 Determining risk of hypoglycemia: questions for the dental patient.

1. Have you ever had severe hypoglycemia?
2. How often do you have hypoglycemic reactions?
3. What diabetic medication(s) do you take?
   Did you take them today?
   When did you take them?
   Is that the same time as usual?
   How much of each medication did you take?
   Is this the same amount you normally take?
4. What did you eat today before you came to the dental office?
   Is that when you normally eat?
   Did you eat the same amount you normally eat for that meal?
   Did you skip a meal?

Table 22-31 Treatment of hypoglycemia in the dental office.

Patient Condition	Treatment
Patient is awake and able to take food by mouth	• Give 15 g oral carbohydrate • 4–6 oz (125–175 mL) fruit juice or soda (nondiet) • 3–4 tsp (equal to 15–20 mL) Table sugar (hard candy, cake frosting)
Patient is unable to take food by mouth and intravenous line is in place	• Give 25–30 mL D50 (50% dextrose solution) or • 1 mg glucagon
Patient is unable to take food by mouth and intravenous line is not in place	• Give 1 mg glucagon subcutaneously or intramuscularly at almost any body site

experiences signs or symptoms of possible hypoglycemia, the dentist should check the blood glucose with a glucometer, which has a typical response time of less than 15 seconds. Rapidly absorbed oral carbohydrates are preferable, particularly if the dentist is not trained or equipped to administer intravenous, intramuscular, or subcutaneous glucagon or dextrose. Following treatment, the signs and symptoms of hypoglycemia should resolve in 10–15 minutes, and the patient should be carefully observed for 30–60 minutes after recovery. A second evaluation with a glucometer should be done to ensure that a normal blood glucose level has been achieved.

A medical emergency from hyperglycemia is less likely to occur in the dental office since it develops more slowly than hypoglycemia. Emergency care entails protecting the airway and administering oxygen. Circulation and vital signs should be monitored, and the patient should be transported to a hospital as soon as possible. However, under some instances, severe hyperglycemia may present with symptoms mimicking hypoglycemia. If it is an actual hyperglycemic event, the small amount of extra glucose delivered will not have any deleterious effect. Nevertheless, emergency measures that will elevate serum glucose should not be delayed or withheld from a DM patient even if hyperglycemia is wrongly suspected in a patient who is actually hypoglycemic. This delay may result in severe adverse outcomes.[186]

Table 22-32 World Health Organization (Who) classification of obesity.

WHO Classification	Body Mass Index (BMI; kg/m^2)	Risk of Comorbidities
Overweight	25–30	Mildly increased
Obese	>30	
Class I	30–35	Likely
Class II	35–40	Very likely
Class III	>40	Very likely and severe
BMI = $\frac{\text{Weight (in kilograms)}}{\text{Height (in meters)}^2}$		

OBESITY

Obesity is defined as an abnormal or excessive fat accumulation such that it impairs health. It is commonly measured by calculating an individual's BMI (Table 22-32).[187]

The prevalence of obesity and the associated comorbidities, particular T2DM, has dramatically increased and has been termed an "obesity epidemic."[188] In the United States, 17% of children and more than 33% of adults are obese, so the problem is common and on the rise (Table 22-33).[188] Although there is ongoing contention as to the etiology of obesity, which includes genetic factors and disturbances of the gut microbiotome, the main factor is an energy imbalance; that is, excessive food intake and insufficient energy expenditure. The comorbidities and complications, including premature death from obesity, are established, with higher rates of DM, coronary heart disease, and cerebrovascular disease.

Metabolic Syndrome

Metabolic syndrome (also known also as "syndrome X" and "insulin resistance"; Table 22-34), in a patient with established obesity, is defined by five factors for increased risk of atherosclerotic cardiovascular disease (which includes consequent coronary heart disease and stroke):

- Atherogenic dyslipidemia comprising elevations in plasma triglycerides and apolipoprotein B (apo B), and reductions in high-density lipoproteins (HDL).
- Hypertension.
- Prediabetes or frank diabetes.
- A prothrombotic state with abnormalities in coagulation factors and blood platelets.
- A proinflammatory state resulting from inflammatory mediators acting on a variety of tissues.

Table 22-33 US data on prevalence of being overweight and of obesity among adults and children.

Prevalence	Class	Body Mass Index (BMI) (kg/m^2)
33%	of adults are overweight	25 to ≤30
36%	of adults are obese	≥30
6%	of adults are morbidly obese	≥40
17%	of children are obese*	25 to ≤30
*BMI for age and sex 95th percentile		
Target BMI is 18.5 to ≤25.0 BMI ≥30.0 + a comorbidity = morbid obesity		
Comorbidities • Hypertension; coronary heart disease; stroke • Sleep apnea • Type 2 diabetes mellitus; dyslipidemia • Osteoarthritis • Reduced fertility • Select cancers		

The contribution of each of these components to cardiovascular risk undoubtedly varies among individuals, but in combination they double the risk for atherosclerotic-related cardiovascular disease and are associated with a fivefold increased risk for diabetes.[189]

Stomatognathic Manifestations and Complications of Obesity[190,191]

Obesity: Clinical Implications

There is a contention that obesity is associated with an increased risk of periodontal disease. The chronic proinflammatory state associated with obesity may increase a patient's susceptibility to periodontal disease, although the published evidence is somewhat contradictory. There is a probable association between obesity and periodontal disease, but not a clear causal relationship. As obesity is associated with a higher intake of sugar, it has been suggested that this may be associated with higher rates of dental caries. Again, the reported studies have yielded contradictory results. There are case reports of higher rates of caries in patients post bariatric surgery, given their need for small, more frequent meals.[192] Dental erosion is related to increased rates of gastroesophageal reflux disease seen in patients with obesity, which is also a known complication of bariatric surgery, but the evidence consists of case reports only.

Concurrent Medical Comorbidities

Obese patients in general and those with metabolic syndrome are known to have a far greater likelihood of hypertension, cardiovascular disease, and T2DM. If these conditions are not identified as being managed by a physician in the course of taking the patient's medical history, it

Table 22-34 Classification systems for metabolic syndrome.

Risk Factor	NCEP 3 of any 6 features		IDF large waist + 2 other features	
Waist Circumference				
Men	>102	cm	>94	cm
Women	>88	cm	>80	cm
Triglycerides	>1.7	mmol/L	≥1.7	mmol/L
HDL Cholesterol				
Men	<1.03	mmol/L	1.03	mmol/L
Women		mmol/L	1.29	mmol/L
Blood Pressure	>130/85	mm Hg	>130/85	mm Hg
Fasting Glucose	≥6.1	mmol/L	≥5.6	mmol/L

HDL, high-density lipoproteins; IDF, International Diabetes Federation; NCEP, National Cholesterol Education Program.
Source: Data from Udovcic M, Pena RH, Patham B, Tabatabai L, Kansara A. Hypothyroidism and the heart. *Methodist Debakey Cardiovasc J.* 2017;13(2):55–59.

Table 22-35 STOP-bang questionnaire: a practical approach to screen for Obstructive Sleep Apnea (OSA).

S	1	Snoring	Do you snore loudly?*	Yes/No
T	2	Tired	Do you often feel tired, fatigued, or sleepy during daytime?	Yes/No
O	3	Observed	Has anyone observed you stop breathing during your sleep?	Yes/No
P	4	Pressure—BP	Do you have or are you being treated for high blood pressure?	Yes/No
B	5	BMI	BMI >35 kg/m^2	Yes/No
A	6	Age	Age ≥50 years of age?	Yes/No
N	7	Neck circumference	Neck circumference ≥40 cm?	Yes/No
G	8	Gender	Male gender?	Yes/No
High risk of OSA: answering yes to 3 or more items				
Low risk of OSA: answering yes to fewer than 3 items				

* E.g., louder than talking or loud enough to be heard through closed doors?
BMI, body mass index; BP, blood pressure.

may be prudent to undertake screening for these conditions before considering highly invasive surgical procedures. Obesity is highly predictive for OSA. The exact interaction between obesity and OSA is unclear. The buildup of adipose tissue in the upper airway predisposes it to collapse and narrowing; however, OSA may itself predispose individuals to worsening obesity due to sleep deprivation, daytime somnolence, and disrupted metabolism. Regardless, OSA is a contraindication to dental sedation; for all patients for whom sedation is being considered, clinicians should employ the STOP-Bang questionnaire (Table 22-35),[193] but particularly so for obese patients.

Weight-Loss Drugs and Potential Drug Interactions

Increasing numbers of patients are using medication to facilitate their weight loss (see Table 22-36). Of these the most notable in the recent past was the advent of the fenfluramine–phentermine (fen–phen) combination, which was associated with valvular heart disease and required affected patients to take antibiotic prophylaxis to limit the risk of infective endocarditis following invasive dental procedures.[194,195]

Orlistat (trade name Xenical®, Roche, Nutley, NJ, USA) is a reversible inhibitor of gastric and pancreatic lipases, thus it inhibits the absorption of dietary fats by 30%.[196] Orlistat can interfere in the absorption and uptake of fat-soluble vitamins, including vitamin K, and consequently can potentiate the anticoagulant effect of warfarin. An update of the patient's international normalized ratio (INR) prior to invasive dental procedures should be considered. Supratherapeutic INR (>4.0) and subtherapeutic INR (<2.0) needs attention by the treating physician.[197]

Lorcaserin (Belviq®, Arena Pharmaceuticals, San Diego, CA, USA) appears to have no major adverse effects and no significant drug interactions. The phentermine–topiramate combination (Qsymia®, Vivus, Campbell, CA, USA) consists of an amphetamine derivative and an antiseizure agent, respectively. Concurrent use of benzodiazepines (and other CNS depressants) with the phentermine–topiramate combination may potentiate CNS depression and should be avoided without medical consultation. With naltrexone–bupropion (Contrave®, Currax Pharmaceuticals, Morristown, NJ, USA), due to the antagonistic effect of naltrexone on endogenous opioid receptors, the analgesic effect of opioid agents is reduced. If opioid analgesia is required in such patients, then temporary cessation of Contrave must be considered.

Issues with Service Delivery

All oral healthcare clinicians have a role in screening for systemic disease and lifestyle factors that are proven to be harmful to a patient's wellbeing, for example smoking and obesity. However, there is a reluctance by dentists to undertake screening and to offer advice regarding the need for and value of weight loss,[198] and so further training and education on how to offer appropriate and acceptable health advice about obesity, and the need for weight loss, may address this concern.

Obesity presents a number of practical challenges to service delivery. The first is the need for longer appointment times, and the consequent increased cost of service delivery. Increased appointment times are attributed to reduced patient mobility as well as increased difficulty for the dentist

Table 22-36 Weight loss medications: major side effects and drug interactions.

Generic Name	Trade Name	Site and Mechanism of Action	Major Side Effects	Drug Interactions
Orlistat	Xenical	• GIT • Lipase inhibitor • Inhibits uptake of dietary fats by 30%	• Steatorrhea • Flatulence	Warfarin
lorcaserin	Belviq	• CNS • Serotonin agonist (5-HT2C receptor agonist) • Increased satiety so reduced food intake	• Headache • Dizziness • Nausea	Benzodiazepams
Phentermine/ topiramate	Qsymia	• CNS • Stimulator of noradrenaline, dopamine, and serotonin release, augmenting the activity of γ-aminobutyrate • Appetite suppression	• Dry mouth • Paresthesia • Constipation • Insomnia • Dizziness	Carbamazepine (decreased topiramate levels)
Naltrexone/ bupropion	Contrave	• CNS • Naltrexone is an opioid antagonist • Bupropion, a relatively weak inhibitor of the neuronal reuptake of dopamine and norepinephrine. • Affects areas of the brain involved in the regulation of food intake: the hypothalamus (appetite regulatory center) and the mesolimbic dopamine circuit (reward system)	• Nausea • Headache • Constipation • Dizziness • Vomiting • Dry mouth • Dysgeusia	Opioid analgesics (less effective)
Liraglutide	Saxenda	• GIT and CNS • Daily subcutaneous injection • Acylated human GLP-1 analogue with 97% homology to human GLP-1 • Like human GLP-1 it increases satiety, decreases key hunger signals, with transient inhibition of gastric emptying	• Nausea • Hypoglycemia • Diarrhea • Constipation • Vomiting	

CNS, central nervous system; GIT, gastrointestinal tract; GLP-1, glucagon-like peptide-1.
Source: Data from RxList. https://www.rxlist.com/script/main/hp.asp.

Figure 22-17 Image of Barico dental chair at Westmead Centre for Oral Health, suitable for all patient groups up to 454 kg. Note the width of the chair (black arrow), especially at the shoulders (white arrows), which makes access to the patient's oral cavity by the treating dentist more difficult. Malik Z. Special needs dental management of the class 3 obese patient. *Case Rep Dent.* 2019;2019:7976531. Reproduced with permission.

in accessing the oral cavity in the larger, obese patient. The other aspect is the need to have equipment that is safe for obese patients. Body weights in excess of 140 kg may exceed the weight limitations of motorized dental chairs.[199–201] Consequently, there are increased costs required to purchase special-purpose and safe bariatric dental chairs (Figure 22-17) and wheelchairs as well as supplementary equipment, including hoists.

DISORDERS OF BONE AND MINERAL METABOLISM

Bone is a specialized connective tissue serving three major functions:

- *Mechanical*: attachment for muscles for movement and structure.
- *Metabolic*: providing the body's primary store of calcium, including a highly active role in calcium homeostasis and also in phosphate levels, as well as serving as a reservoir for sodium, magnesium, and other critical ions.

- *Protective*: of the vital organs as well as enclosing the marrow, containing the essential hematopoietic stem cells that produce all the cells found circulating in the blood (red blood cells, leukocytes, and platelets).

Bone comprises cells and a matrix of organic protein and hydroxyapatite crystal. Type I collagen is the main protein, forming parallel lamellae of differing density, which impair the propagation of cracks with trauma. Noncollagen proteins that are also found in bone include osteopontin, osteocalcin, and fibronectin. In cortical bone, concentric lamellae form around a central blood supply, and this collectively is termed the Haversian system, with transverse branches (termed Volkmann's canals). The long bones (e.g., femur, tibia, humerus) and flat bones (e.g., skull, scapula) are variably composed of:

- *Compact or cortical bone*, which forms the shaft of long bones and the outer shell of flat bones. Formed of concentric rings of bone, it is strong and is particularly resistant to the mechanical strain associated with flexure.
- *Trabecular or cancellous bone*, found at the ends of long bones and inside flat bones, is constituted by a network of interconnecting rods and plates of bone that provides great strength against compressive forces. It is the main site of bone turnover needed for mineral homeostasis.
- *Woven bone* lacks an organized structure. It appears in the first few years of life and at the sites of fracture repair, as well as in bone disorders associated with high turnover, such as Paget's disease. Woven bone is eventually remodeled to be organized and structurally sound bone.
- *Lamellar bone*, in which the collagen fibers are arranged in parallel bundles, forms much of the bone found in adults.

Bone Cells

Osteoblasts are of mesenchymal origin and are initially found on the surface of newly forming bone. The osteoblast secretes an organic matrix, which then is mineralized, encasing the cell, which is then termed an *osteocyte*; however, the osteocytes remain connected with each other, as well as with their blood supply, through a fine network of canaliculi, distributed throughout the bone. The vast majority of the cells found in bone are osteocytes, which serve to regulate bone formation and resorption and also serve as mechanosensors, signaling the osteoblasts and their progenitors through the canalicular network. Mineralization of the matrix, both in trabecular bone and in the osteones (of the Haversian system) of compact cortical bone, begins soon after the matrix is secreted and is termed primary mineralization, but it is not completed for several weeks or even longer by the process of secondary mineralization. Mineralization is a carefully regulated process that is dependent on the activity of osteoblast-derived alkaline phosphatase, and importantly the very high, near-saturation concentrations of calcium and phosphate present in the serum. Hormones such as parathyroid hormone (PTH) and 1,25-dihydroxyvitamin D (1,25(OH)2D) activate receptors expressed by osteoblasts so as to regulate mineral homeostasis.

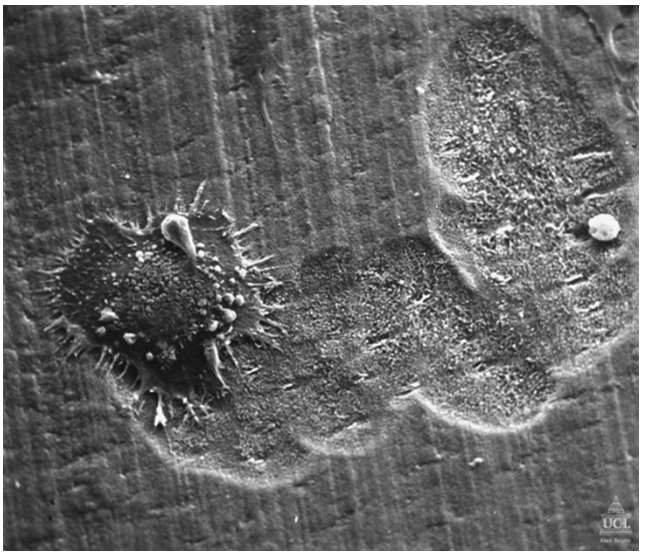


Figure 22-18 Osteoclast. *Source:* Bone Research Society, https://boneresearchsociety.org/resources/gallery/19/. Reproduced with permission.

Osteoclasts (Figure 22-18) serve to resorb bone, and are multinucleated cells that are formed by the fusion of cells derived from the same common precursor of macrophages. Multiple factors regulate osteoclast development and function. Macrophage colony-stimulating factor (M-CSF) plays a critical role during several steps in the pathway and ultimately leads to the fusion of osteoclast progenitor cells to form multinucleated, active osteoclasts. RANK (receptor activator of nuclear factor kappa-B) ligand is a member of the tumor necrosis factor (TNF) family, expressed on the surface of osteoblast progenitors and stromal fibroblasts. In a process involving cell–cell interactions, RANK ligand binds to the RANK receptor on the osteoclast progenitors, stimulating osteoclast differentiation and activation. Alternatively, a soluble decoy receptor, referred to as osteoprotegerin (OPG), can bind the RANK ligand and so inhibits osteoclast differentiation. OPG, also known as osteoclastogenesis inhibitory factor (OCIF), is a cytokine receptor and also a member of the TNF receptor superfamily. Several growth factors and cytokines can also modulate osteoclast differentiation and function (e.g., interleukins 1, 6, and 11, TNF, and interferon γ); they may also have role in the bone loss seen

in periodontal disease. Most hormones that influence osteoclast act indirectly, by influencing M-CSF and RANK ligand signaling of the osteoblasts. Both PTH and 1, 25(OH)2D increase osteoclast number and activity, whereas estrogen decreases osteoclast number and activity. Calcitonin, in contrast, binds directly to its receptor on the basal surface of osteoclasts and so inhibits osteoclast function. Osteoclast-mediated resorption of bone takes place in scalloped spaces (Howship's lacunae) where the osteoclasts are attached through a specific αvβ3 integrin to components of the bone matrix, such as osteopontin.[202]

Bone Growth and Remodeling

In the embryo and the growing child, bone develops by remodeling and replacing previously calcified cartilage, termed endochondral bone formation, or bone is formed without a cartilage matrix anlage, by means of intramembranous bone formation. Longitudinal growth occurs at the epiphyseal growth plate, a cartilaginous structure between the epiphysis and the metaphysis. Cartilage production is tightly regulated, with growth arrest and the subsequent mineralization occurring between the ages of 18 to 21 years, when the epiphysis and metaphysis plates fuse.

In adults, bone is constantly being remodeled, to repair microdamage and for the release of the calcium and phosphate needed for homeostasis. Signals regulating the initiation of remodeling include changes in osteocytes (apoptosis or altered signaling of sclerostin, prostaglandins, and other molecules), resulting in altered balance of RANK ligand and OPG expression by adjacent osteoblasts. Remodeling is carried out by the basic multicellular unit (BMU). Normal bone remodeling is a coupled process, with bone formation typically following resorption. New bone formation without resorption may, however, occur in the adult skeleton in response to anabolic therapy such as PTH peptides or estrogen (in both sexes), which is particularly involved by promoting the survival of osteocytes and inhibiting the formation of new osteoclasts.

Calcium Homeostasis

Over 99% of the 1–2 kg of calcium normally present in the adult human body resides in the skeleton, where it provides mechanical stability (in the form of hydroxyapatite) and also serves as a reservoir for maintenance of extracellular fluid (ECF) calcium concentration (Figures 22-19 and 22-20; Table 22-37). Only some 0.5–1% of the skeletal calcium is

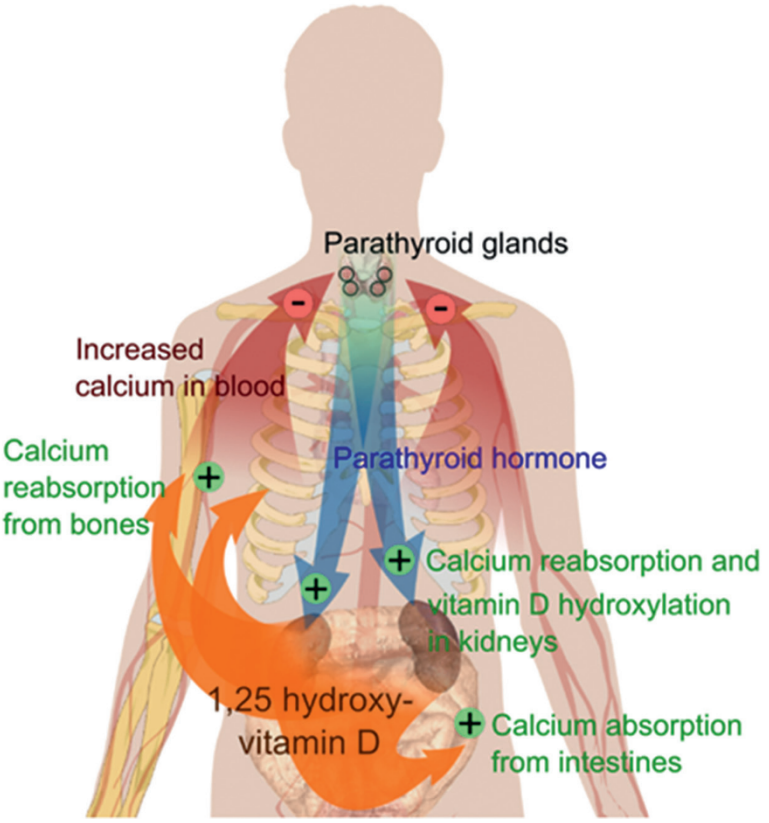


Figure 22-19 Calcium regulation and homeostasis. *Source:* https://commons.wikimedia.org/wiki/File:Calcium_regulation.png. Public domain.

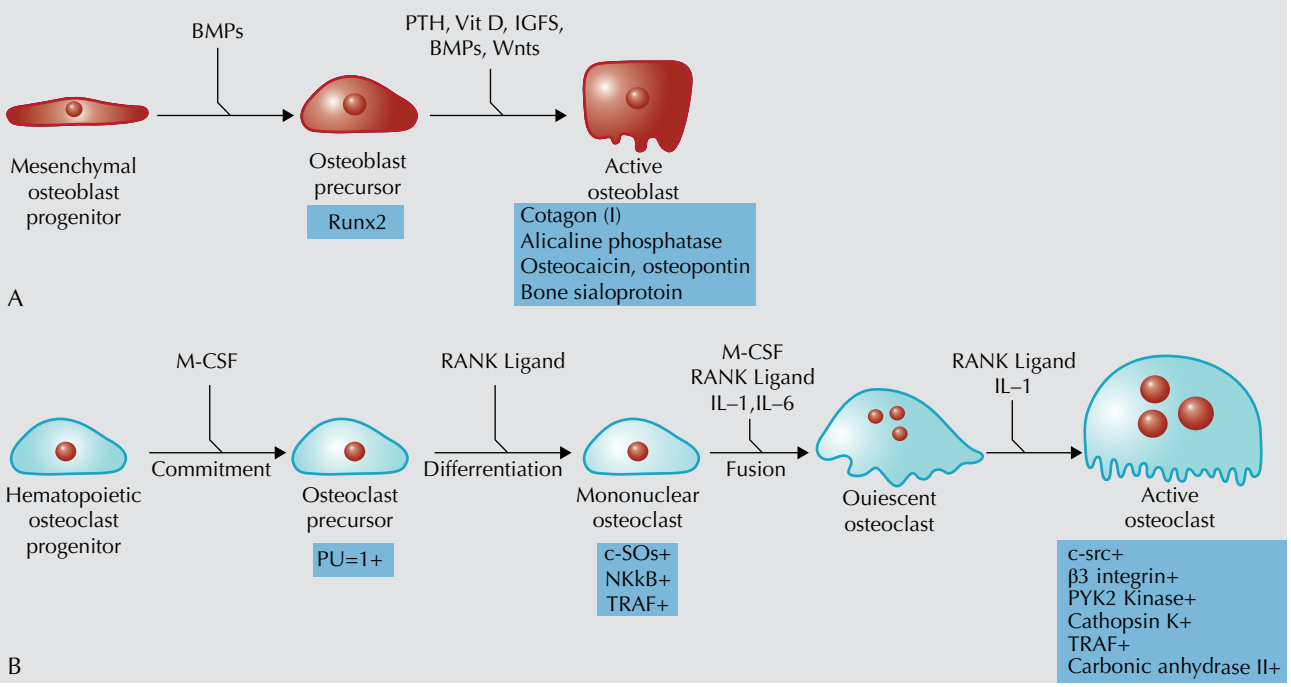


Figure 22-20 Pathways regulating development of (A) osteoblasts and (B) osteoclasts. Hormones, cytokines, and growth factors that control cell proliferation and differentiation are shown above the arrows. Transcription factors and other markers specific for various stages of development are depicted below the arrows. BMPs, bone morphogenic proteins; IGFs, insulin-like growth factors; IL-1, interleukin 1; IL-6, interleukin 6; M-CSF, macrophage colony-stimulating factor; NFκB, nuclear factor κB; PTH, parathyroid hormone; PU-1, a monocyte- and B lymphocyte–specific ETS family transcription factor; RANK ligand, receptor activator of NFκB ligand;Runx2, Runt-related transcription factor 2; TRAF, tumor necrosis factor receptor–associated factors; Vit D, vitamin D; wnts, wingless-type mouse mammary tumor virus integration site. *Source:* Adapted with permission from Suda T, Takahashi N, Udagawa N, Jimi E, Gillespie MT, Martin TJ. Modulation of osteoclast differentiation and function by the new members of the tumor necrosis factor receptor and ligand families. *Endocr Rev.* 1999;20:345.

freely exchangeable; that is, in chemical equilibrium with the calcium found in the ECF. The concentration of ionized calcium in the ECF is maintained within a strict narrow range, because of the critical role it plays in numerous critical cellular functions, particularly neuromuscular activity, secretion, and signal transduction. In the blood, total calcium concentration is normally 2.2–2.6 mM (8.5–10.5 mg/dL), of which some 40% is ionized and physiologically active. The remaining 60% is bound to negatively charged proteins (predominantly albumin and immunoglobulins) or loosely complexed with phosphate, citrate, sulfate, or other anions. Alterations in serum protein concentrations (e.g., hypoalbuminemia) directly affect the total blood calcium concentration, but the ionized calcium concentration tends to remain stable.

Control of the ionized calcium concentration in the ECF is regulated by the effects of PTH and 1,25(OH)2D3 acting on the gastrointestinal tract, kidney, and bone. Ionized calcium in the circulation both directly suppresses PTH secretion by stimulating the calcium-sensing receptors present in the parathyroid glands, and indirectly suppresses PTH secretion via effects on vitamin D_2 (1,25(OH)2D) production. Active calcium uptake from the gut by means of highly regulated, energy-dependent transportation across the gut epithelium accounts for up to 95% of the daily calcium intake needed. This occurs mainly in the proximal small bowel (duodenum and proximal jejunum). Calcium absorption may also be impaired in disease states such as pancreatic or biliary insufficiency, in which ingested calcium remains bound to unabsorbed fatty acids or food debris, conditions associated with gastrointestinal malabsorption, such as in celiac disease and in patients who have had an extensive bowel resection. At high levels of calcium intake, synthesis of 1,25(OH)2D is reduced and this then decreases the rate of active intestinal calcium absorption.[203]

Daily net calcium absorption is generally constant at 5–7.5 mmol/day (equal to 200–400 mg/day), regardless of variations in the daily dietary calcium intake. This daily load of absorbed calcium is excreted by the kidneys in a tightly regulated manner, with approximately 8–10 g/day of calcium being filtered by the glomeruli, of which only 2–3% appears in the urine. Most filtered calcium (65%) is reabsorbed in the proximal tubules via a nonregulated, passive, paracellular

Table 22-37 Investigation of bone and calcium disorders.

Test	Normal Values	Interpretation/Considerations
Total serum calcium (corrected) (Ca^{2+})	2.2–2.6 mmol/L	Total serum calcium (corrected) • 40% is ionized and physiologically active Note: ionized calcium is difficult to measure; in practice total calcium is measured and the value corrected to allow for protein binding (using established formula)
24-hour urinary calcium	F: 2.5–6.25 mmol/24 h M: 2.5–7.5 mmol/24 h	Indications: hypercalcemia ↑ Renal tubular reabsorption of Ca^{2+} is decreased ↑ Hypercalcemia: exception with familial hypocalciuric hypercalcemia—genetic defect leads to inappropriately reduced calcium excretion
Plasma phosphate (PO_4^{3-}) levels	0.8–1.4 mmol/L	↑ [PO_4^{3-}] • Renal failure and hypoparathyroidism ↓ [PO_4^{3-}] • Primary hyperparathyroidism • Hypophosphatemic rickets • Osteomalacia • Disorders of reduced renal tubular phosphate reabsorption
Serum alkaline phosphatase (ALP)	• Bone-specific isoenzyme of ALP can be measured (marker of bone formation), but there is overlap with the liver isoenzyme	↑ ALP • Bone growth • Fracture repair • High bone turnover states
Vitamin D	• Best assessed using serum 25-(OH)D3 Note: 1,25(OH)2D3 has a short half-life and does not reflect true vitamin D status	
Parathyroid hormone	• Measures intact hormone	
NTX or CTX—serum or urine levels	• N-terminal (NTX) and C-terminal (CTX) cross-linked telopeptides ➔ Reflect bone resorption activity	↓↑ Changes rapidly in response to antiresorptive drugs or in disease states
Bone mineral densitometry (BMD)	• Dual-energy X-ray absorptiometry (DXA): uses low-dose radiation to measure areal bone density—mineral per surface area (rather than true volumetric density) • Sites: lumbar spine, proximal femur	Note: Gold standard for the diagnosis of osteoporosis • Young adult mean value (T score) is the standard • Spinal values may be artefactually elevated with osteophytes, spinal deformity, and vertebral fractures (so interpret with caution in the elderly)

route that is coupled to concomitant sodium chloride (NaCl) transporter. The remaining 35% requires active reabsorption in the thick loop of Henle and distal tubule.

Vitamin D Metabolism

The primary source of vitamin D in humans is photoactivation in the skin of 7-dehydrocholesterol to cholecalciferol, which is then converted, first in the liver to 25-hydroxyvitamin D (25(OH)D3) and then subsequently in the kidney (by the enzyme 1α hydroxylase) to the active form, 1,25(OH)2D3. Regulation of the latter step is by PTH, phosphate, and feedback inhibition by 1,25(OH)2D3 itself.

The mounting concern about sun (ultraviolet, UV) exposure and the development of skin cancer has led to increased reliance on dietary sources of vitamin D. The third National Health and Nutrition Examination Survey (NHANES) revealed that vitamin D deficiency is widely prevalent in the United States. Vitamin D deficiency can be a result of deficient production of vitamin D in the skin (insufficient UV exposure), lack of dietary intake, accelerated losses of vitamin D, impaired vitamin D activation, or resistance to the biologic effects of 1,25(OH)2D. The elderly and nursing home residents are particularly at risk for vitamin D deficiency, since both the efficiency of vitamin D synthesis in the skin and the absorption of vitamin D from the intestine

decline with age. Long-standing vitamin D deficiency results in hypocalcemia accompanied by secondary hyperparathyroidism, impaired mineralization of the skeleton—termed osteopenia; that is, decreased bone mineral density (BMD)—with a resultant increased risk for progression to osteoporosis.

Parathyroid Hormone

PTH, an 84 amino acid hormone, is secreted from the chief cells of the parathyroid glands, which bear calcium-sensing and vitamin D receptors. PTH increases renal phosphate excretion and increases plasma calcium by four principal effects: increasing osteoclastic activity—a rapid response; increasing intestinal absorption of calcium—a slow response; increasing 1α-hydroxylation of vitamin D (the rate-limiting step); and increasing renal tubular reabsorption of calcium. Hypomagnesemia can suppress the normal PTH response to hypocalcemia.

Calcitonin

Calcitonin is produced by C cells in the thyroid gland. Although calcitonin inhibits osteoclastic bone resorption and increases the renal excretion of calcium and phosphate, neither excess calcitonin (e.g., from an MTC) nor its deficiency (following thyroidectomy) appears to have any significant effect on the skeleton or bone density. Calcitonin is a useful agent to suppress bone resorption in Paget's disease and osteoporosis and in the treatment of hypercalcemia of malignancy.

Sclerostin

Sclerostin is a glycoprotein secreted by osteocytes. Sclerostin has been shown to be a potent inhibitor of bone formation by means of a catabolic effect on bone, increasing osteoclast numbers and activity by augmented osteocyte expression of the RANK ligand. Significant research interest in this signaling pathway led to the evolution of antisclerostin agent; that is, inhibitory therapeutic antibody, romosozumab. Of note is that a decline in RANK ligand signaling could explain, in part, the sustained decreases in bone resorption markers observed in recent trials with antisclerostin therapies.[204]

The role of sclerostin in the modulation of the Wnt/β-catenin dependent pathway came from the study of sclerosteosis and van Buchem disease, two rare genetic disorders associated with abnormally high levels of bone density and consequently a significantly lower risk of bone fractures.[205] Both diseases were traced to mutations impacting a single gene, *SOST*, which is mainly expressed from osteocytes. The Wnt signaling pathway is a crucial, ancient, and evolutionarily conserved pathway that regulates key aspects of cell fate determination, cell migration, cell polarity, neural patterning and organogenesis during embryonic development. The Wnt signaling pathway has a significant interaction with a transmembrane lipoprotein receptor-related protein, LRP5. The *LRP5* gene was initially identified as a determinant of bone mass in the 1990s from studies into osteoporosis pseudoglioma syndrome, an autosomal recessive hereditary disorder (characterized by low bone mass and abnormal eye vasculature), due to an inactivation mutation of *LRP5*.[206] In contrast, gain-of-function *LRP5* mutations are linked to the autosomal dominant condition of high bone mass, excessive bone formation, bone thickening, and reduced risk of fracture.[207] These findings were confirmed in mouse models of defective Wnt signaling. *LRP5*-deficient mice manifested an osteoporotic phenotype with impaired bone formation, while bone resorption remained unaffected. In contrast, mice carrying an gain-of-function mutation within the *LRP5* gene developed thick abnormal bone (osteosclerosis).[208,209] Sclerostin production by osteocytes is inhibited by PTH, mechanical loading, and select cytokines, such as prostaglandin E2. Sclerostin production is increased by calcitonin. Thus, osteoblast activity is self-regulated by a negative feedback system involving sclerostin.[210,211]

Based on genetic and rat studies, a monoclonal antibody directed against sclerostin has been developed. Romosozumab (marketed as Evenity® in the United States; Amgen, Thousand Oaks, CA, USA) gained FDA approval in April 2019, albeit with black box warning of increased risk for myocardial infarction, stroke, and cardiovascular-related death and that the drug should not be taken by patients who had experienced a cardiovascular event within the previous year.[212] Romosozumab is given by monthly subcutaneous injection and has shown great promise, with one large trial indicating significant benefit in reducing vertebral fractures in osteoporotic women.[213] However, two cases of osteonecrosis of the jaws (ONJ) occurred in the romosozumab-treated cohort of 3321 women (0.06%) over the course of 12 months.[214]

PARATHYROID GLAND AND DISORDERS OF CALCIUM HOMEOSTASIS

PTH is secreted by four parathyroid glands found within the thyroid gland in the anterior neck. Secretion of the PTH is in response to the level of serum ionized calcium. Low serum ionized calcium stimulates PTH secretion, whereas high serum ionized calcium suppresses PTH secretion. Another major regulator of PTH is the active form of vitamin D_3 (1,25-dihydroxyvitamin D_3 or calcitriol). It suppresses PTH

synthesis by its ability to promote intestinal calcium absorption. PTH protects the body from chronic low serum calcium (hypocalcemia); therefore, an individual with chronic hypocalcemia and vitamin D deficiency may develop parathyroid gland hyperplasia.

Hyperparathyroidism

Hyperparathyroidism is chronic excessive secretion of the PTH by the parathyroid glands. It results in uncontrolled chronic high serum calcium (hypercalcemia). The condition occurs in 0.1% of adult patients, is more common in the third to fifth decades of life, and is three times more prevalent in women than in men. The vast majority (90%) of patients with hypercalcemia have either primary hyperparathyroidism or hypercalcemia of malignancy.

Primary hyperparathyroidism is the term that refers to excessive PTH secretion arising from one or more of the parathyroid glands. Commonly it is caused by a solitary adenoma (80% of cases), whereas 15% are due to parathyroid hyperplasia and 1% are due to carcinoma of the parathyroid glands. Postmenopausal women are more commonly affected by primary hyperparathyroidism.[215]

Secondary hyperparathyroidism occurs with compensatory parathyroid gland enlargement in response to persistent hypocalcemia induced by renal failure (see later), or metabolic disorders of deficiency of 1,25(OH)2D, or malabsorption of calcium found in rickets and some forms of osteomalacia. PTH secretion from enlarged parathyroid glands may become autonomous (secreting without control or response to feedback inhibition), leading to *tertiary hyperparathyroidism*.[216]

Many cases of hyperparathyroidism may be asymptomatic and only detected incidentally by serum analysis during routine serologic evaluation. Clinically, patients may have manifestations of skeletal and renal disorders and hypercalcemia. They complain of a classic quintet of complaints, namely "bones, stones, abdominal groans, psychic moans, and psychic overtones." Skeletal presentations include bone demineralization that manifests as a reduction in bone mass (osteopenia). Bone radiographs show well-circumscribed unilocular or multilocular radiolucent lesions, known as "brown tumors" of hyperparathyroidism, but brown tumors are now rare because of early detection of hyperparathyroidism. Due to routine screenings and early detection of hypercalcemia, skeletal presentation is now commonly just as osteopenia. Renal presentations include polyuria and polydipsia as a result of hypercalcemia-induced DI, and 10–15% of patients may develop kidney stones consisting of calcium phosphate or calcium oxalate. Nonspecific presentations of hypercalcemia include "abdominal groans" of constipation, indigestion, weight loss, nausea, vomiting, peptic ulceration, and pancreatitis, as well as "psychic moans" of lethargy, fatigue, depression, loss of memory, paranoia, neuroses, change in personality, confusion, stupor, and coma.

The most common laboratory finding is high alkaline phosphatase in patients with bone lesions. Serum calcium is elevated (>10.5 mg/dL), but phosphate may vary from low-normal (<3.5 mg/dL) to low (<2.5 mg/dL). Serum PTH is often elevated, and the level of 1,25(OH)2D may also be high due to the stimulatory effect of PTH on 1-α-hydroxylase. Imaging should be undertaken to assess for the presence of a parathyroid adenoma. For symptomatic primary hyperparathyroidism, definitive treatment is surgical parathyroidectomy, which has a 95% success rate. Medical management may involve use of vitamin D when associated with vitamin D deficiency, as well as bisphosphonates and calcimimetics and the calcium-sensing receptor agonist cinacalcet (Sensipar®, Amgen). As postmenopausal women are commonly affected by hyperparathyroidism, high-dose estrogen replacement therapy is often needed to treat bone lesions and reduce serum calcium, but it does not reduce the PTH level.

Hypoparathyroidism

Hypoparathyroidism is a deficiency in the production, secretion, or action of PTH and is the most common cause of hypocalcemia. It usually results when parathyroid glands are surgically removed to correct primary hyperparathyroidism or during thyroidectomy. Radiation to the neck, metastatic cancer, infection, and magnesium deficiency are other unusual causes of hypoparathyroidism. Damage to the parathyroid glands by heavy metals, for example copper in Wilson's disease or iron in hemochromatosis, and from transfusion hemosiderosis is also an unusual cause of hypoparathyroidism. The parathyroid glands may be underdeveloped or completely absent in DiGeorge syndrome (now more accurately known as 22q11.2 deletion syndrome), a developmental abnormality of the third and fourth pharyngeal pouches.[217] *Pseudohypoparathyroidism* is a term used to describe a group of disorders that cause hypocalcemia as a result of renal resistance to PTH despite high levels of PTH. Other causes of hypocalcemia in addition to hypoparathyroidism are vitamin D deficiency, hyperphosphatemia, malabsorption of calcium, and chronic renal failure.[218]

Hypocalcemia

Hypocalcemia is often asymptomatic; however, acute hypocalcemia produces symptoms that result from neuromuscular irritability or excitability. This leads to muscular and mental manifestations that include paresthesia of hands, feet, and

circumoral muscles; electroencephalographic abnormalities; anxiety; confusion; and depression. A positive Chvostek's sign may be elicited by tapping on the facial nerve in the preauricular region, which causes twitching of the facial muscles. Patients may develop tetany characterized by tonic–clonic seizures, carpopedal spasm, and severe laryngospasm. In DiGeorge syndrome, tetany is usually noticed in infancy, but may remain undetected until adulthood. Laboratory findings are low PTH and low serum calcium levels, but serum phosphate is elevated and alkaline phosphatase is normal. Most patients with hypocalcemia can be treated with oral calcium and vitamin D supplements, although acute cases may require intravenous calcium infusions.

Chronic Renal Failure

Impaired production of 1,25(OH)2D by the diseased kidneys is thought to be the principal factor that causes calcium deficiency, secondary hyperparathyroidism, and bone disease. Treatment entails dietary changes, with the restriction of phosphate in the diet, avoidance of aluminum-containing phosphate-binding antacids to prevent the problem of aluminum intoxication, adequate calcium intake orally, usually 1–2 g/day, and supraphysiologic amounts of vitamin D or calcitriol, despite the fact that the uremic state also causes impairment of intestinal absorption of vitamin D. The aim is to restore normal calcium balance to prevent osteomalacia and severe secondary hyperparathyroidism.

Stomatognathic Manifestations of Parathyroid Gland Disorders

Hyperparathyroidism

The primary clinical orofacial signs and symptoms of hyperparathyroidism are reflections of the systemic effects of hypercalcemia. Long-standing hypercalcemia causes generalized osteoporosis, which is visible on dental radiographs. Patients develop cortical resorption and rarefactions, loss of trabeculation presenting as "ground-glass" appearance, partial or total loss of lamina dura, lytic lesions, and metastatic calcifications.[219] The rarefactions occur secondary to generalized osteoporosis when fine trabeculae disappear later in the disease process, leaving a coarse pattern. Alveolar bone is particularly sensitive to increased levels of PTH from either primary or secondary hyperparathyroidism.[220] Thinning and eventual loss of the cortical bone of the maxilla and mandible may occur, especially on the lower border of the mandible. Severe cases may result in spontaneous mandibular fracture.[221]

Stomatognathic Manifestations and Dental Management

Children with rickets/osteomalacia may present with delayed tooth eruption, loss of lamina dura, and enamel and dentine hypoplasia that may progress to periapical infections. Malocclusion and hypoplastic teeth increase the risks of dental caries; therefore, regular oral health evaluation is necessary to monitor dental and periodontal health.

OSTEOPOROSIS

Osteoporosis is defined as "a disease characterized by low bone mass and micro-architectural deterioration of bone tissue, leading to enhanced bone fragility and an increase in fracture risk."[222] The World Health Organization (WHO) defines osteoporosis as a bone density of 2.5 standard deviations (SDs) below the young healthy adult mean value (T score ≤ -2.5) or lower. Values between -1 and -2.5 SDs below the young adult mean are termed "osteopenia."

Fractures due to osteoporosis are a major cause of morbidity and mortality in elderly populations and a major contributor to rising health costs. Osteoporotic fractures of the spine cause severe, acute pain or deformity and postural back pain. The risk of fracture increases exponentially with age, with 1 in 2 women and 1 in 5 men aged 50 years having an osteoporotic fracture during their remaining lifetime (Table 22-38). Caucasian and Asian races are particularly at risk.

Osteoporosis occurs from increased bone breakdown by osteoclasts and decreased bone formation by osteoblasts, leading to loss of bone mass. Bone mass decreases with age, but will depend on the "peak" mass attained in adult life (at about the age of 40–45 years) and on the rate of loss in later life. The main risk factor for osteoporosis is estrogen deficiency. In the elderly, vitamin D insufficiency and consequent hyperparathyroidism are of greater importance. Hyperparathyroidism, hyperthyroidism, and malabsorption all increase the lifetime risk of a person having a low bone mass and low BMD. Additional risk factors associated with increased bone loss, or with increased bone fragility, include

Table 22-38 Hip fractures per 1000 patient-years.

World Health Organization Category	50–64 Years of Age	>64 Years of Age	Overall
Normal	5.3	9.4	6.6
Osteopenia	11.4	19.6	15.7
Osteoporosis	22.4	46.6	40.6

Source: Cranney A, Jamal SA, Tsang JF, Josse RG, Leslie WD. Low bone mineral density and fracture burden in postmenopausal women. *Canadian Med Assoc J.* 2007;177(6):575–580.

glucocorticoid therapy and smoking. Falls increase the risk of fracture, on top of the risk associated with the particularly low bone mass. Osteoporosis is asymptomatic, except subsequent to a fracture. Bone density assessment by use of dual-energy X-ray absorptiometry (DXA) is the gold standard for the diagnosis of osteoporosis.

Prevention and Treatment of Osteoporosis (and Consequent Fractures)

Exercise

Life-long weight-bearing exercise, as little as 30 minutes, three times a week, may increase BMD. Gentle exercise in the elderly reduces the risk of falls and improves the protective reflexes needed with falling.

Smoking Cessation

This should be strongly encouraged, as smoking is associated with lower BMD and increased fracture risk.

Reduced Alcohol Intake

Alcohol intake of >3 units/day should be avoided.

Fall Reduction

This can be assisted with physiotherapy and assessment of home safety, with installation of hand rails and nonslip floor surfaces, especially in wet areas such as the bathroom and toilet.

Vitamin Supplementation

Calcium

Research has established that optimal calcium intake reduces bone loss and suppresses bone turnover. For men and women aged 19–50 years the recommended daily intake is 1000 mg/day, and for adults 51 years and older this should be increased to 1200 mg/daily. The best sources are dairy foods, but many patients require calcium supplementation.

Vitamin D

The US Institute of Medicine recommends 200 IU/daily for adults <50 years of age, 400 IU/daily for those 50–70 years, and 600 IU for those >70 years.

Pharmacologic Interventions

See Table 22-39.

Estrogen(s)/Hormone Replacement Therapy

Given the adverse effects of an increased risk for breast cancer and cardiovascular disease risk, hormone replacement therapy (HRT) is a second-line option for osteoporosis, except in younger postmenopausal women at high fracture risk.

Selective Estrogen-Receptor Modulators

Raloxifene 60 mg daily is a selective estrogen-receptor modulator (SERM) that has the advantage of having no stimulatory effect on the endometrium, but activates estrogen receptors in bone. It prevents BMD loss of bone from the spine and hip in postmenopausal women. It also reduces the incidence of estrogen-receptor-positive breast carcinoma in women treated for up to 4 years. Leg cramps and flushing may occur and the risk of thromboembolic complications is also increased, including stroke, to a degree similar to that seen with HRT.

Antiresorptive Agents

Bisphosphonates

These synthetic analogues of bone pyrophosphate adhere to hydroxyapatite and inhibit osteoclasts (Tables 22-40 and 22-41). Alendronate, risedronate, and ibandronate are approved for the prevention and treatment of postmenopausal osteoporosis in the United States. Aclasta® (zoledronic acid; Novartis Europharm, Frimley, UK) infusion is approved for use in the treatment and prevention of osteoporosis in the United Kingdom and Europe. Risedronate and alendronate are approved for the treatment of steroid-induced osteoporosis. Bisphosphonates are generally well tolerated, but the orally given agents are associated with upper gastrointestinal side effects, such as esophagitis. Bisphosphonates given as an infusion negate the gastrointestinal side effects and ensure patient compliance, thus they are increasingly popular for the management of osteoporosis, apart from their established role in malignancy-associated bone diseases (hypercalcemia, bony metastases, and multiple myeloma). The optimal duration of bisphosphonate therapy is unknown, with prolonged suppression of bone turnover having adverse effects, including atypical, low-impact, femoral fractures, and ONJ. Current recommendations are to reassess the need for ongoing bisphosphonate treatment after 3–5 years, although the benefits appear to exceed the risk of these complications.

Denosumab

Sold as Prolia® (Amgen) when used for osteoporosis (in contrast to Xgeva® [Amgen] when used in the setting of malignancy), this is a fully human monoclonal antibody to RANK ligand. It is given twice yearly by subcutaneous administration for osteoporosis. Randomized controlled trials in postmenopausal women with osteoporosis have shown it to increase BMD in the spine, hip, and forearm and reduce vertebral, hip, and nonvertebral fractures over a 3-year period by 70%, 40%, and 20%, respectively. Fracture risk reduction is equivalent to bisphosphonates. Interestingly, the risk for osteonecrosis is equivalent to that seen with the more potent bisphosphonates, comparable with the use of zoledronic acid, in the setting of malignancy.

Table 22-39 Drug therapies used for osteoporosis.

Oral Agents

Class	Actions	Generic Name	Trade Name(s)[a]	Indications	Disadvantages/ Warnings
Minerals and Vitamins					
Calcium	• Essential for bone mineral formation	Calcium carbonate Calcium citrate	Various (plus, various combinations with vitamin D)	Aids in prevention and treatment of osteoporosis	
Vitamin D3	• Maintenance of skeletal calcium • Promotes calcium absorption from gastrointestinal tract • Maintains calcium and phosphate levels for bone formation • Proper function of parathyroid hormone (PTH)	Cholecalciferol (vitamin D3) Calcitriol (1,25-dihydroxy-vitamin D3), active form of D3	Various (plus various combinations with calcium)	Aids in prevention and treatment of osteoporosis	• Hypervitaminosis D (daily allowance:15 µg/d (600 IU/d • Excess of vitamin D: ➔ hypercalcemia ➔ overcalcification of the bones, soft tissues, heart and kidneys ➔ Damage to kidney ➔ Kidney stones
Estrogen/Estrogen-Related Agents					
Hormone replacement therapy	• Effect of estrogen is to inhibit bone resorption • With estrogen deficiency, the osteoclasts live longer and are therefore able to resorb more bone	Conjugated estrogens	Premarin	Prevention of postmenopausal osteoporosis	Risks: ↑ Myocardial infarction ↑ Stroke ↑ Pulmonary embolism (PE) and deep vein thrombosis (DVT) ↑ Breast cancer ? Dementia
Selective estrogen-receptor modulators	• Acts as estrogen agonist in bone ↓ Decreases bone resorption ↓ Bone turnover ↓ Decreases fracture incidence ↑ Bone mineral density	Raloxifene	Evista	Treatment and prevention of osteoporosis in postmenopausal women Reduction in risk of invasive breast cancer	Risks: ↑ DVT, PE ↑ Stroke ↑ Major coronary event
Antiresorptive Agents					
Bisphosphonates (amino-bisphosphonates)	• At the cellular level, preferential localization to sites of bone resorption, specifically under osteoclasts	Alendronate Risedronate Ibandronate	Fosamax Binosto Actonel Atelvia Boniva	Treatment and prevention of osteoporosis in postmenopausal women, men, and glucocorticoid-induced osteoporosis Paget's disease	• Optimal duration of use not determined • Patients at low risk for fracture, consider drug discontinuation after 3–5 years • Osteonecrosis of the jaw (ONJ)

Parenteral Agents (Intravenous, Intramuscular, and/or Subcutaneous)

Class	Actions	Generic Name	Trade Name(s)[a]	Indications	Disadvantages/ Warnings
Antiresorptive Agents					
Bisphosphonates	• in vitro, zoledronic acid inhibits osteoclastic activity and induces osteoclast apoptosis	Zoledronic acid	Reclast	Treatment and prevention of postmenopausal osteoporosis, for men, and glucocorticoid-induced osteoporosis Paget's disease 5 mg every 1–2 years	• ONJ
Denosumab	• Prolia binds to receptor activator of nuclear factor kappa-B (RANK) ligand • Protein essential for formation, function, and survival of osteoclasts ↓ Osteoclast formation, function, and survival, thereby decreasing bone resorption and increasing bone mass and strength	densumab	Prolia	Treatment and prevention of postmenopausal osteoporosis, for men, and glucocorticoid-induced osteoporosis 60 mg subcutaneously (SQ) every 6 months	• Prevention of skeletal-related events in patients with cancer: 120 mg SQ every 4 weeks • ONJ (incidence similar to that of zoledronic acid)
Calcitonin	• Hormonal bone resorption inhibitor; action on bone has not been fully established	Calcitonin (salmon rDNA) Intranasal/ intramuscular/SQ	Fortical Miacalcin	Treatment of postmenopausal osteoporosis in women >5 years post menopause in conjunction with Ca^{2+} and vitamin D	
Teriparatide (Forteo) Recombinant human PTH	↑ New bone formation by stimulation of osteoblastic activity over osteoclastic activity ↑ Skeletal mass ↑ Markers of bone formation and resorption ↑ Bone strength	20 μg daily SQ		Treatment of postmenopausal women with osteoporosis, men with primary or hypogonadal osteoporosis, and glucocorticoid-induced osteoporosis for patients at high risk for fracture	• Not to be prescribed for patients who are at increased baseline risk for osteosarcoma (including those with Paget's disease)

→ leads to; ↑, increases; ↓ , decreases; ?, uncertain.

Table 22-40 Bisphosphonates: indications and usage.

Usage	Indication	Comments	Incidence of MRONJ
>90%	Osteoporosis (>90% usage)	• Postmenopausal • Corticosteroid induced/related • "Male" age-related osteoporosis • Renal osteodystrophy • Male hypogonadism	<10%
~1%	Other/rare conditions	• Paget's disease • Osteogenesis imperfecta • Reflex sympathetic dystrophy (complex regional pain syndrome) • Heterotopic ossification with spinal cord injury • Total hip replacement • Giant cell tumor of bone	
5–10%	Malignancy	Skeletal (bony) metastases (from solid malignancies • Breast cancer • Lung cancer • Prostate cancer Multiple myeloma Hypercalcemia	>90%

MRONJ, medication-related osteonecrosis of the jaws.

Table 22-41 Amino-bisphosphonates and their potency ratings.

Nitrogenous (N-Containing) Bisphosphonates

Generic Name	Trade Name	R2 Group	Potency
Pamidronate	Aredia	Amino	100
Alendronate	Fosamax	Amine	1000
Ibandronate	Bondronate	Long-chain nitrogen	10 000
Risedronate	Actonel	Cyclic nitrogen	10 000
Zoledronate	Zometa	Cyclic nitrogen	>10 000

Potency is calculated on the agents' antiresorptive effect on bone, i.e., the decline in bone resorption.
Source: Adapted from Licata AA. Discovery, clinical development, and therapeutic uses of bisphosphonates. *Ann Pharmacotherapy*. 2005;39(4):668–677.

Calcitonin

Calcitonin preparations are approved by the FDA for Paget's disease, hypercalcemia, and osteoporosis in women more than 5 years post menopause. Calcitonin suppresses osteoclast activity by direct action on the osteoclast calcitonin receptor. Calcitonin produces small increments in bone mass of the lumbar spine. A nasal spray (Fortical®, Upsher-Smith Laboratories, Minneapolis, MN, USA) containing calcitonin (200 IU/day) is available for treatment of osteoporosis in postmenopausal women and as an injectable form (Miacalcin®, Mylan Pharmaceuticals, Canonsburg, PA, USA).[223]

Teriparatide

Teriparatide (Forteo®, Eli Lilly, Indianapolis, IN, USA) is recombinant human parathyroid hormone (rhPTH) peptide 1–34, an anabolic agent that stimulates bone formation. Teriparatide reduces vertebral and nonvertebral fractures in postmenopausal women with established osteoporosis, although data on hip fracture are not yet available. It is given by daily subcutaneous injection in a dose of 20 μg for 18–24 months. rhPTH therapy is indicated in severe cases of vertebral osteoporosis or in women who fail to respond to other therapies.[224]

Antisclerostin Antibody Agents

Romosozumab only gained FDA approval in April 2019. It is given as a monthly subcutaneous injection (see earlier).

Glucocorticoid-Induced Osteoporosis

Iatrogenic osteoporosis is a recognized major complication of the therapeutic use of glucocorticoids. The risk of fractures depends on the dose and duration of glucocorticoid therapy, although data now suggest that there may be no completely safe dose.

Patients needing continuous oral glucocorticoid therapy for 3 months or more (at any dose) should be assessed for coexisting risk factors (age, previous fracture, and hormone status). Postmenopausal women and men aged over 50 years, as well as any individuals who have sustained a fracture, should receive treatment for the prevention of osteoporosis

and its progression, without waiting for BMD assessment. To date, only bisphosphonates have been demonstrated in large clinical trials to reduce the risk of fractures in patients being treated with glucocorticoids. Calcium and vitamin D supplementation also needs to be given.

MEDICATION-RELATED OSTEONECROSIS OF THE JAWS

Medication-related osteonecrosis of the jaws (MRONJ) is a clinical entity in which patients develop localized areas of bone necrosis involving the jawbones, predominantly the mandible, and the maxilla (Figures 22-21 and 22-22).[225] The necrosis, which is the key feature seen with MRONJ, entails cell and tissue injury, resulting in unexpected, premature cell death by an as yet unclear process, although necrosis usually results from trauma, infection, and/or toxins within otherwise unaffected, vital, normal bones of the jaws. Hence, the abbreviated term *osteonecrosis of the jaws* (ONJ) is also used.

There are select medications that have been established to be strongly associated with MRONJ. Of these, the drugs with the greatest and most frequently described associations are those that act to inhibit bone resorption, termed antiresorptive agents. They include the following drugs (or classes of drug):

- Amino-bisphosphonate agents.
- Denosumab, a monoclonal antibody directed against the RANK ligand found on osteoclasts.
- Romosozumab, the first of a new class of antisclerostin antiresorptive agents.[226]
- Antiangiogenic agents, which interfere with the formation of new blood vessels (angiogenesis) that is essential for cancer growth and development. A number of these agents alone, but more commonly when given concurrently with antiresorptive agents, have been associated with the development of MRONJ (Table 22-42).[227–229]

Of note is that other agents that affect bone remodeling and turnover—that is, teriparatide (the humanized recombinant form of human PTH) and strontium ranelate (never marketed in the United States because of the significant adverse risks of heart attacks and blood clots)—are not associated with MRONJ. Strontium ranelate has a dual action stimulating both osteoclastic and osteoblastic activity, and teriparatide is known to have a similar effect, given its anabolic effect on bone turnover. Of interest is that teriparatide has in a small number of case reports shown to be of benefit in established MRONJ.[234–239]

Evolution of the Nomenclature

Until the advent of the antiresorptive agent denosumab in 2010,[240] and reporting of the association between denosumab and ONJ,[241] ONJ was exclusively associated with bisphosphonate agents, and specifically the newly introduced, more potent amino-bisphosphonates. The initial bisphosphonate with a side chain containing nitrogen, termed an amino-bisphosphonate, was pamidronate, which was approved for medical use in 1987.[242] Subsequently, further modification of the nitrogen-containing side groups resulted in newer, highly potent agents with regard to their ability to prevent bone resorption by their interference in that action

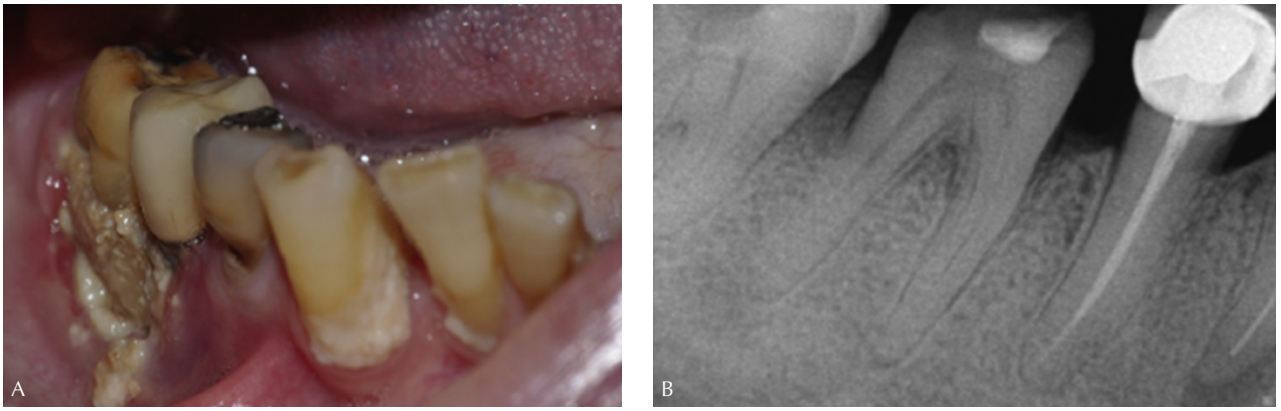


Figure 22-21 Example of exposed medication-related osteonecrosis of the jaw. A patient receiving high-dose denosumab presented with pain of 6 months' duration on the right lower first molar. He was receiving antibiotics. (A) Exposed bone and purulence were observed on the buccal alveolar bone area of the tooth consistent with osteonecrosis of the jaw, exposed type, before dental extraction. (B) Panoramic radiography disclosed alveolar bone loss around the molar tooth. Courtesy of Professor Ourania Nicolatou-Galitis, Dental School, National and Kapodistrian University of Athens. *Source:* Nicolatou-Galitis O, Schiødt M, Mendes RA, et al. Medication-related osteonecrosis of the jaw: definition and best practice for prevention, diagnosis, and treatment. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2019;127(2):117–135.

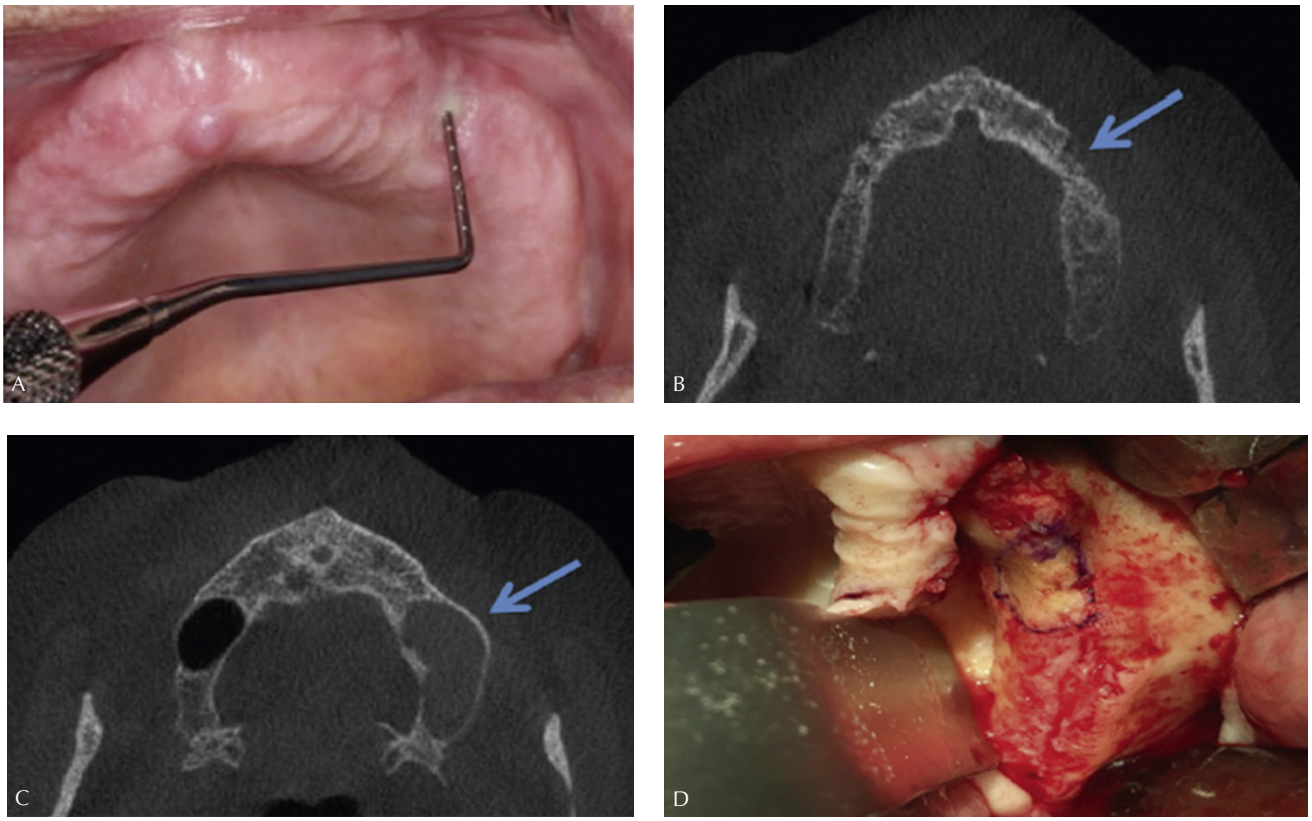


Figure 22-22 Example of nonexposed medication-related osteonecrosis of the jaw. (A) A patient receiving high-dose denosumab presented with pain in an apparently normal edentulous left maxilla. A droplet of pus was seen on palpation and bone was probed through a fistula. (B, C) Cone-beam computed tomography showed sequestrum at regions 24 and 25 (arrow) and infection in the left maxillary sinus. (D) Perioperative view showing osteonecrosis outlined on the bone surface. Uneventful healing was accomplished. Courtesy of Dr. Morten Schiødt, University Hospital of Copenhagen. *Source:* Schiødt M, Wexell CL, Herlofson BB, Ottesen C, Nørholt S-E. Medicinrelateret osteonekrose i kæberne—oversigt og retningslinjer. *Tandlægebladet*. 2015;119:918–930. Published with the permission of the Danish Dental Journal.

and also reducing the number of osteoclasts. Hence there is now widespread use of these potent amino-bisphosphonate agents to treat and prevent osteoporosis, which is caused by relatively excessive bone resorption by osteoclasts that is not matched by bone formation by osteoblasts. Of the amino-bisphosphonates, the most potent is zoledronic acid (zoledronate), marketed as Zometa® and Reclast® (Novartis Pharmaceuticals, East Hanover, NJ, USA), which was introduced in 2001.[243] MRONJ was first reported in 2003.[244] Given that up to 2010 the only drugs shown to be consistently associated with ONJ were bisphosphonates, the term bisphosphonate-related osteonecrosis of the jaws (BRONJ) was adopted, including variations such as bisphosphonate-associated osteonecrosis of the jaws (BAONJ), bisphosphonate-associated osteonecrosis (BON), osteochemonecrosis of the jaws (OCNJ), and "bis-phossy jaw." However, the term medication-related osteonecrosis of the jaws is now preferred and MRONJ has replaced BRONJ, since it has been recognized that ONJ is associated with other agents besides bisphosphonates, including the newer antiresorptive agent denosumab and antiangiogenic agents used in the treatment of various cancers.

Case Definition

The case definition and established diagnostic features of MRONJ are as follows:

- Current or previous treatment with bisphosphonates and/or denosumab, as well as select antiangiogenic agents. However, generally MRONJ occurs when these select antiangiogenic agents have been used concurrently with an antiresorptive agent.
- A localized area of exposed bone, or bone that can be readily probed through fistula, which can be intraoral or extraoral (i.e., through the skin overlying the mandible or maxilla, the nasal cavity of adjacent maxillary sinuses) and has been present or persistent for more than 8 weeks.
- No history of prior radiation therapy to the jaws.
- Exclusion of obvious metastatic disease or deposits of the jaws.

Table 22-42 Antiangiogenic agents associated with medication-related osteonecrosis of the jaws (MRONJ).

Drug	Mechanism of Action	Primary Indication	
Sunitinib (Sutent)	• Tyrosine kinase inhibitor (TKI) • Sunitinib inhibits cellular signaling by targeting multiple receptor tyrosine kinases, including: – Platelet-derived growth factor receptors (PDGFR) – Vascular endothelial growth factor receptors (VEGFRs), which play a role in tumor angiogenesis and cell proliferation[230]	GIST RCC pNET	Gastrointestinal stromal tumor Renal cell carcinoma Pancreatic neuroendocrine tumor
Sorafenib (Nexavar)	• TKI • Sorafenib is a protein kinase inhibitor with activity against many protein kinases, including: – VEGFR – PDGFR – RAF kinases (three serine/threonine-specific protein kinases related to retroviral oncogenes)[231]	HCC RCC	Hepatocellular carcinoma Renal cell carcinoma
Bevacizumab (Avastin)	• Bevacizumab is a recombinant humanized monoclonal antibody that blocks angiogenesis by inhibiting: – Vascular endothelial growth factor A (VEGF-A)[232]	mCRC NSCLC Glio mRCC	Metastatic colorectal carcinoma Nonsquamous non-small-cell lung carcinoma Glioblastoma Metastatic renal cell carcinoma
Sirolimus (Rapamune)	• Mammalian target (mTor) of rapamycin pathway • Downregulates the expression of these VEGFs by decreased expression of both the proteins and mRNA: – VEGF-A/VEGFR-2 and VEGF-C/VEGFR-3,which are closely involved in angiogenesis and lymphangiogenesis[233]	Prevention of rejection in renal transplantation	

Source: Adapted from Ruggiero SL, Dodson TB, Fantasia J, et al. American Association of Oral and Maxillofacial Surgeons position paper on medication-related osteonecrosis of the jaw—2014 update. *J Oral Maxillofac Surg*. 2014;72(10):1938–1956.

The case definition has evolved, with the recognition that metastatic disease or deposits of the jaws are important differential diagnoses that need to be considered and excluded, which is best done by histopathologic assessment following biopsy.[245] Caveats apply to this case definition, including increasing recognition of cases in which exposed bone for protracted periods is not necessarily the presenting feature of MRONJ.[246–247]

Staging

The American Association of Oral and Maxillofacial Surgeons staging system of 2014[227] serves to define cases and the severity of the MRONJ identified, but stage-specific treatment approaches have a sound and growing evidence base as to their effectiveness (Table 22-43).[248]

Definitions of High-Dose versus Low-Dose Antiresorptive Therapy

The epidemiology for MRONJ has clearly established that 90% of cases occur in patients with cancer receiving *high-dose* therapy; that is, intensive dosing regimens of intravenous, high-potency bisphosphonates, mainly zoledronic acid (4 mg every 3–4 weeks) or subcutaneous denosumab (120 mg every 4 weeks). Data from prospective studies demonstrated that properly adjudicated MRONJ occurred in 1.3% of cancer patients treated with zoledronic acid and in 1.1% of patients with cancer treated with denosumab.[249] Furthermore, the evidence demonstrates that the increase in the cumulative dose of antiresorptive agent is associated with an increasing incidence of MRONJ. Among patients

Table 22-43 Staging of medication-related osteonecrosis of the jaws (MRONJ).

Stage	Findings
Patients at risk	No apparent necrotic bone in asymptomatic patients who have been treated with intravenous or oral antiresorptive or antiangiogenic therapy
Stage 0 (Nonexposed bone variant)	Patients with no clinical evidence of necrotic bone, but present with nonspecific symptoms or clinical and radiographic findings: **Symptoms** • Odontalgia not explained by an odontogenic cause • Dull, aching bone pain in the body of the mandible, which may radiate to the temporomandibular joint region • Sinus pain, which may be associated with inflammation and thickening of the maxillary sinus wall • Altered neurosensory function (patients may complain of altered sensation of the lips) **Clinical findings** • Loosening of teeth not explained by chronic periodontal disease • Periapical/periodontal fistula not associated with pulpal necrosis due to caries **Radiographic findings** • Alveolar bone loss or resorption not attributable to periodontal disease • Changes to bony trabecular pattern: – Dense woven bone – Persistence of unremodeled bone in extraction sockets • Regions of osteosclerosis involving the alveolar bone and/or the surrounding basilar bone • Thickening/obscuring of periodontal ligament: – Thickening of the lamina dura – Decreased size of the periodontal ligament space[150]
Stage 1 (Asymptomatic)	• Exposed and necrotic bone or fistulae that on probing contacts bone, in patients who are asymptomatic and have no evidence of infection. **Radiographic findings**: as seen in Stage 0, may also be present that are localized to the alveolar bone region
Stage 2 (Symptomatic)	• Exposed and necrotic bone *and/or* • Fistulae that on probing contacts bone, with evidence of infection • Patients are symptomatic • **Radiographic findings**: as seen in Stage 0, may also be present that are localized to the alveolar bone region
Stage 3	Exposed and necrotic bone, or fistulae that probe to bone, with evidence of infection and one or more of the following: • Exposed necrotic bone extending beyond the region of alveolar bone – to the inferior border and ramus in the mandible – maxillary sinus and zygoma in the maxilla • Pathologic fracture • Extraoral fistula • Oral antral/oral nasal communication • Osteolysis extending to the inferior border of the mandible or sinus floor

Source: Adapted from Ruggiero SL, Dodson TB, Fantasia J, et al. American Association of Oral and Maxillofacial Surgeons position paper on medication-related osteonecrosis of the jaw—2014 update. *J Oral Maxillofac Surg*. 2014;72(10):1938–1956.

with advanced breast cancer with bony metastases, the incidence of MRONJ at years 1, 2, and 3 was 0.5%, 1.2%, and 1.4%, respectively in those patients who received zoledronic acid, and 0.8%, 1.9% and 2.0%, respectively in those treated with denosumab. The risk of ONJ among patients with cancer exposed to antiresorptive or antiangiogenic medications is about 1%, but ranges between 0.2% and 6.7%.[250] Overall, the benefit provided by antiresorptive therapy outweighs the

risk of development of MRONJ in the settings of both osteoporosis and oncology.

Low-dose antiresorptive medication regimens are those typified by the dosing regimens for osteoporosis in postmenopausal women, which includes oral and intravenous bisphosphonates, with an example of the latter being zoledronic acid (5 mg every 12 months) and denosumab at a dose of 60 mg every 6 months.[251] Such low-dose regimens dominate the use, dose, and frequency of antiresorptive agents for all of their approved indications, *except* in the setting of patients with cancer. It is estimated that over 90% of patients taking antiresorptive agents are receiving low-dose regimens. The risk of ONJ among patients who are managed for osteoporosis using antiresorptive medications is about 0.1% (range 0.004%–0.2%), but this increase, as seen with patients taking oral bisphosphonates to manage osteoporosis with the risk of ONJ after tooth extraction, is estimated to be 1 in 200 (0.5%).[252] However, as has been established, it is not only the intensity of the antiresorptive dosing regimen that affects the rate of MRONJ, it is the overall cumulative dose. For patients receiving oral bisphosphonate therapy to manage osteoporosis, the prevalence of ONJ increases over time from near zero to 0.2% after 4 or more years of bisphosphonate exposure, with ONJ being seen at a median duration of oral bisphosphonate exposure of 4.4 years. Although there is less published data, the same phenomenon was seen in osteoporotic subjects taking denosumab. After 2 years of exposure, the incidence of ONJ was 0.09%, but this doubled to 0.2% after 6 years of exposure to denosumab.[253]

The significance of this epidemiologic evidence regarding the risk and duration of antiresorptive treatment associated with the development of MRONJ is as follows:

- In the majority of patients taking antiresorptive agents, these are low-dose regimens associated with a modest to significantly lower risk of MRONJ occurring.
- Regardless of which antiresorptive agent is involved, patients who are taking these drugs in the setting of cancer have a significantly greater risk of developing MRONJ, >1%, and this risk increases with the greater cumulative dose of the agent taken.
- There are definite "window periods" in which patients on low-dose antiresorptive drug regimens remain at a very low risk for MRONJ, which appears to be up to 4 years of treatment with low-dose antiresorptive agents. In this period, invasive dental procedures such as extractions (and implant placement) can be undertaken with a low risk of MRONJ occurring.

For dentists, this represent a critical period in which patients need to be made as dentally fit as possible, providing patients on such antiresorptive agents with a sustainable and easily maintainable dentition that negates the need for future dental extractions.

Window Periods for Patients on High-Dose Antiresorptive Therapy

The epidemiologic data indicate that up to 4 years of treatment with a low-dose antiresorptive treatment regimen, whether it be an oral or intravenous bisphosphonate agent or denosumab, is associated with very low risk of MRONJ occurring, even with the undertaking of invasive procedures, namely extractions. These data can be extrapolated and applied to patients who are on high-dose antiresorptive therapy in the setting of cancer. The cumulative 4-year low-dose regimen of any specific antiresorptive agent is indicative of the cumulative dose at which the risk of MRONJ substantially increases. This, by way of specific examples, is 20 mg of zoledronic acid (equal to 4 years of treatment at 5 mg per annum) and 480 mg for denosumab (equal to 4 years of treatment at 120 mg per annum; 60 mg given every 6 months). In the setting of cancer, patients will be exposed to 20 mg of zoledronic acid after 15 weeks. The standard dosing regimen for zoledronic acid used in cancer patients is 4 mg every 3 weeks, therefore it will take 15 weeks (~3.5 months) for a dose of 20 mg to be reached. For patients taking denosumab in the setting of cancer, it will take 16 weeks to reach a dose of 480 mg, as denosumab is given at 120 mg every 4 weeks. Note that in a setting of hypercalcemia of malignancy, "loading" doses of 120 mg of denosumab are to be given on days 8 and 15 within the initial 4 weeks, so shortening the tine to reach 480 mg to just 4 weeks; that is, one month. At 4 weeks a patient will have taken 240 mg, with 120 mg of denosumab given on days 0 and 28 and an extra 240 mg (2×120 mg) on days 8 and 15.

This extrapolation of the data suggests that for patients needing zoledronic acid or denosumab for the prevention of skeletal-related events of bony metastases or of the progression of the bony lytic lesions of multiple myeloma, but not when denosumab is used to treat hypercalcemia of malignancy, there is a potential window period of up to 3 months. Within this 3-month window, invasive dental procedures can be undertaken in an effort to make the patient dentally fit and so preventing the need for extractions after the 3-month window expires. However, there is no direct evidence in the form of patient-based studies that have established this premise, which is based on first principles.

Risk Factors

The overriding factor for the assessment of the risk of MRONJ developing is cumulative exposure of the patient to bisphosphonates or denosumab, considering both the dose per treatment and the number of administrations given from the start of the treatment.[254] A secondary consideration should be the relative potency of the agents used. Although to date no clear threshold dose below which MRONJ does

not occur has yet been identified, consensus is emerging in the setting of patients receiving low-dose antiresorptive medication for osteoporosis: some experts argue that the risk of MRONJ is significant after 3 years of therapy,[245] while the American Academy of Oral and Maxillofacial Surgery has stated that for patients who have received 4 years of low-dose antiresorptive treatment, the risk of MRONJ occurring subsequent to invasive dental procedures is low.[227]

The other major risk factors are the presence of infection, since typically MRONJ develops following a local infection and/or trauma to bone or soft tissues, as occurs with invasive dental procedures, namely extractions. Recent data have shown that localized periodontal or dental disease may precede the appearance of MRONJ.[37] Furthermore, alveolar bone necrosis has been documented at the time of dental extraction and the bacterial microbiotome within the necrotic bone is consistent with that seen in periodontal disease.[255,256] Dentists should be aware of the risk of MRONJ when considering invasive procedures (e.g., tooth extraction or implant placement), in cases of pressure sores from ill-fitting dentures, and when there is significant inflammation/infection.[112–114] Other factors have also been associated with an increased risk of MRONJ, including the use of other cancer therapies and/or previous or concurrent corticosteroid use, smoking, poor oral hygiene, and comorbidities, such as diabetes mellitus and renal failure. In particular, the concomitant use of antiresorptives with agents that inhibit angiogenesis—that is, the formation of new blood vessels as part of tumor growth and spread—has been documented to increase the likelihood of MRONJ occurring.[83]

Treatment Goals

The major goals of treatment for patients at risk of developing or who have MRONJ are as follows:

- Education and engagement with patients and their physicians regarding the risks of MRONJ, how these risks can be ameliorated, and keeping them apprised of when MRONJ occurs and how it can be best managed.
- Prioritization and support of the ongoing treatment for oncology patients requiring high-intensity antiresorptive agents and/or antiangiogenic drugs and those on long-term antiresorptive drugs for osteoporosis (that is, beyond 4 years of treatment). It should be noted that oncologic patients and osteoporotic patients obtain significant therapeutic benefit from antiresorptive therapy by controlling bone pain and lowering the incidence of other skeletal complications and osteoporotic-related fractures.
- For patients on antiresorptive agents that have not exceeded the window periods, prioritizing their dental care, removing all immediate and potential likely sources of dental-related infection, and ensuring these patients have a dentition that is sustainable and maintainable, so limiting the need for dental extractions in the future, beyond the designated window periods.

Prevention

Poor dental health—that is, active periodontal disease, and/or infectious and inflammatory complications of caries-induced pulpitis—is an established risk factor for the development of MRONJ in patients on long-term antiresorptive therapy. The converse also applies, in that excellent levels of dental health, supported by preventative dental health measures, have been shown to significantly limit the risks of development of MRONJ, even in patients receiving antiresorptive therapy in the setting of malignancy. This concept needs to be extended, with dental practitioners needing to be mindful of providing a dentition that patients are best able to maintain and that negates the need for future invasive dental procedures, such as extractions or implant placement, given that patients will be in receipt of antiresorptive therapy for long durations (in excess of 5 years) until their BMD score is normalized. For patients who need invasive dental treatment, the risk of such treatment needs to be carefully balanced against the possible risks of such patients developing MRONJ; however, deferring extractions of teeth with a poor to dismal prognosis that are otherwise unrestorable, or unmaintainable, is also associated with risk. In such situations, the presence of ongoing infection and associated inflammation in itself increases the risk of MRONJ occurring, with "spontaneous" cases of MRONJ having been well documented, occurring in 30% of patients without any invasive dental treatment having been undertaken. Patients will continue to receive further antiresorptive treatment for their osteoporosis, as the risks of serious bone fracture and its morbid and possible fatal complications outweigh the risks and complications, such as ONJ.

The risk of MRONJ is now thought to occur in a dose-dependent manner; that is, the greater the dose, the greater the risk of MRONJ occurring. Therefore, it may serve the patient better to undertake the necessary extractions in a planned, preemptive fashion, whereby the risk of MRONJ may be mitigated, than to await a time that extraction becomes inevitable or severe infection develops. Methods to mitigate MRONJ from occurring include the use of a course of pre- and postprocedural antibiotics, with frequent use of antibacterial (chlorhexidine-containing) mouthwashes, a "gentle"—that is, as atraumatic as practical—extraction or oral surgical technique, and primary closure. Such measures may not prevent MRONJ from developing, but may see only MRONJ stage 0 or 1 developing, which is highly amenable to conservative and modest surgical interventions.

Tables 22-44, 22-45, 22-46, and 22-47 estimate and attempt to stratify the risk of MRONJ occurring with invasive dental

Table 22-44 Duration of antiresorptive therapy (in cancer) that is equal to 4 years of treatment for osteoporosis.

Agent	Route of Administration	Osteoporosis Dose Regimen	Total Dose at 4 years	Cancer Dosing Regimen	Duration of Antiresorptive Treatment That Reaches 4-year Total Dose (as for Osteoporosis)	
Zoledronate (Aclasta)	IV	5 mg/year	20 mg	4 mg every 3 weeks	• 20 mg/4 mg = 5 doses • 5 doses given every 3 weeks = 15 weeks **= 3.5 months**	**3 months**
Ibandronate (Bondronat)	IV	3 mg every 3 months	48 mg	6 mg every 4 weeks	• 48 mg/6 mg = 8 doses • 8 doses given every 4 weeks = 32 weeks **= 7 months**	**7 months**
Ibandronate (Bondronat)	Oral	150 mg every month	200 mg	50 mg every day	• 200 mg/50 mg = 144 doses • 144 doses daily = 20 weeks **= 4.6 months**	**4 months**
Pamidronate (Aredia, Pamisol)	IV	60 mg every month	880 mg	90 mg every 3 weeks	• 880 mg/90 mg = 32 doses • 32 doses every 3 weeks = 96 weeks **= 22 months**	**22 months**
Denosumab (Prolia)	SQ	60 mg every 6 months	480 mg	120 mg every 4 weeks	• 480 mg/120 mg = 4 doses • 4 doses every 4 weeks = 16 weeks **= 3.6 months**	**3 months**

IV, intravenous; SQ, subcutaneous.
Source: Prevention of osteonecrosis of the jaw (ONJ) in patients on bisphosphonate therapies. http://www.health.nsw.gov.au/policies/gl/2010/pdf/GL2010_010.pdf

Table 22-45 Bisphosphonates and estimated "window periods" for substantively increased risk of medication-related osteonecrosis of the jaws (MRONJ) with invasive dental procedures.

Name	Generic Name	Route of Administration	Indication	Window Period: Duration of Bisphosphonate Therapy (in Months)*
Zometa	Zoledronic acid	Intravenous	Malignancy-related skeletal events	3
Bondronat	Ibandronate	Intravenous		7
Aredia Pamisol	Pamidronate	Intravenous		22
Bondronate	Ibandronate	Oral		4
Didronel	Etidronate	Oral	Paget's disease; heterotopic ossification with spinal cord injury; total hip replacement	36–48
Zometa	Zoledronic acid	Intravenous	Osteoporosis (noniatrogenic) treatment/ prophylaxis	>36–60?
Aredia Pamisol	Pamidronate			
Actonel	Risedronate	Oral		
Fosomax	Alendronate			

* In which invasive treatment (dental extractions/oral surgery) can be undertaken with a relative lower risk of complications, but not with no risk—risk of MRONJ still is present.
?, uncertain.

procedures. For moderate-risk patients, all the interventions suggested in Table 22-48 should be undertaken and, of course, extensive consultation with the patient's treating physician, and the patient themselves, including providing detailed and informed consent of the risks of MRONJ occurring. For patients stratified (Table 22-46) as being at high risk for developing MRONJ, the risks of the development of MRONJ, versus the benefits of addressing active pain or infection arising from the involved tooth/teeth, need to be outlined. Furthermore, referral of such patients to clinicians and/or specialized centers experienced in the management of MRONJ should be considered.

There also remains considerable doubt regarding the value of "drug holidays" for patients with established MRONJ.[257] However, on discussion with the patient's treating physician, an inquiry regarding the use of non-antiresorptive agents with no known risk for ONJ associated with their use (e.g., teriparatide) may prompt consideration of such alternate agents, especially in those patients with a high risk of developing MRONJ, or who have established MRONJ but still require further invasive dental procedures, such as extractions.

Unfortunately, to date there appear to be no reliable investigations for determining the optimal time to proceed with invasive dental procedures in patients taking antiresorptives. Biochemical markers of bone remodeling, such as CTx and NTx—the cleaved ends of strands of type 1 collagen that are present in the blood and can be assessed on serology, and are indicative of bone turnover—but this test has not been shown to be reliable in determining the risk for MRONJ occurring; therefore, preprocedural serum testing is not presently recommended.[258–262]

Established Medication-Related Osteonecrosis of the Jaws

See Table 22-49. Initially conservative measures only should be undertaken, namely observation. If signs of infection are evident, such as active suppuration or the development of facial swelling, in keeping with an abscess or collection with marked regional lymphadenopathy, then provide the patient with antibiotics: amoxicillin in combination with metronidazole, or a macrolide (e.g., roxithromycin) with metronidazole or clindamycin. Clindamycin has the advantage of coverage of both gram-positive streptococci and anaerobic bacterial species and good bone penetrance. Tetracyclines also have excellent bone penetrance, but bacterial resistance is common, limiting these agents' effectiveness. Frequent use of topical antibacterial mouthwashes, such as chlorhexidine-containing mouthwashes, should also be instituted.

Table 22-46 Risk assessment for medication-related osteonecrosis of the jaws (MRONJ).

Patient-Related Factors	Procedural (Surgical) Factors
Amino-bisphosphonate • Potency • Route of administration • Duration • Clinical indication/usage **Comorbidities** • Age • Diabetes mellitus (poorly controlled) • Immunosuppression	• One or more surgical sites • Contiguous teeth or multiple separate sites • Extent of surgery • Mandibular posterior (molar) teeth • Proximity of tori
Low-risk patient • Low-dose antiresorptive therapy (e.g., osteoporosis) • For no more than 4 years	**Low-risk procedure** • Routine dental extraction • Facilitated by local anesthetic in the dental chair • Up to 3 contiguous teeth
High-risk patient • Patient on long-term/high-dose antiresorptive therapy related to malignancy: – Solid cancer metastases (breast, prostate) – Multiple myeloma • Concurrent administration of antiangiogenic agents • Patients aged >70 years • Immunosuppression • Recent (within 2 weeks) cytotoxic chemotherapy (with resultant leukopenia) • High-dose corticosteroid administration • Diabetes mellitus (poorly controlled)	**High-risk procedure** • Extensive oral surgery • Extensive number of dental extractions – 5 teeth or more – >1 dental quadrant • Surgical extraction of mandibular molar teeth with risk of impinging lingual cortical plate and/or the mylohyoid ridge • Surgery with risk of impinging of maxillary or mandibular tori

Table 22-47 Risk calculator for medication-related osteonecrosis of the jaws (MRONJ).

Risk	Patient-Related Risk Factors	+	Surgical Procedure Risk Factors	
Minimal	Low-risk patient	+	Low-risk procedure	• Provide dental treatment required • If undertaking extractions/oral surgery, monitor regularly for development of MRONJ
Significant	Low-risk patient High-risk patient	+ +	High-risk procedure Low-risk procedure	• **Seek expert guidance** of an oral and maxillofacial surgeon (OMFS) or an oral oncology center with experience in the management of patients with MRONJ
Highly significant	High-risk patient	+	High-risk procedure	• **Refer the patient** to an OMFS or an oral oncology center with experience in the management of patients with MRONJ

DISORDERS OF INTERMEDIATE METABOLISM

Inheritable Disorders of Connective Tissue: Skeletal Dysplasia

These include a large group of heterogeneous disorders of collagen adversely affects the proper development of bone and the connective tissues. All have considerable stomatognathic manifestations and complications.

Marfan's Syndrome

Marfan's syndrome (MFS) is one of the most common autosomal dominant inherited disorders of connective tissue, affecting approximately 1 in 5000 of the population worldwide, with some 25% of individuals having developed MFS as a consequence of a new mutation.[263] It causes cardiovascular problems, especially of the heart, with sufferers developing aortic aneurysms and dissection, which can be fatal, mitral valve prolapse, and a typical body habitus consisting of a tall thin body, with long arms, legs, and fingers; scoliosis and problems with their eyes, such as dislocated lenses and retinal detachment.

Investigations

Investigations are centered on the cardiovascular system and the heart:

- Imaging: chest X-ray may be normal, but often there are signs of aortic aneurysm, widening of mediastinum, and pneumothorax is a common complication, as is scoliosis. Computed tomography (CT) is useful to detect aortic dilatation and for monitoring its progression.
- Echocardiography demonstrates mitral valve prolapse and mitral regurgitation in the majority of patients.
- Electrocardiography (ECG): 40% of patients usually have arrhythmia, with premature ventricular tachycardia and atrial arrhythmias.

Table 22-48 Interventions to mitigate the risk of medication-related osteonecrosis of the jaws (MRONJ).

Antibacterial mouthwashes	Pre- (up to 7 days) and postprocedural (up to 7 days), frequent (daily) and after meals
Antibiotics	Pre- (up to 7 days) and postprocedural (up to 7 days)
Antibiotic regimens Amoxicillin 500 mg 3 times/day) + metronidazole 400 mg 3 times/day Roxithromycin 150 mg twice/day + metronidazole 400 mg 3 times/day Clindamycin 300 mg daily (5 days only)	

Management

- Beta blocker therapy slows the rate of dilatation of the aortic root.
- Sedentary activities are encouraged because of the potential adverse effects of exertion on the heart, pain and potential deformities of the joints, and risk of retinal detachment and lens displacement.
- Annual or more frequent echocardiograms to monitor aortic root dilatation. If the aortic root diameter exceeds 5 cm, this is an indication for aortic root replacement surgery.

Stomatognathic Manifestations and Complications

- Hypermobility with dislocation of the temporomandibular joint.

Table 22-49 Stage-specific treatment for medication-related osteonecrosis of the jaws (MRONJ).

Staging of MRONJ		Recommended Treatment/Treatment Provider	
Stage 0	• No clinical evidence of necrotic bone *but* • Nonspecific clinical findings, radiographic changes, and symptoms	• Antibacterial mouth rinse • Quarterly follow-up/review • Patient education and review of indications for continued antiresorptive therapy • Symptomatic treatment with oral antibiotics and antibacterial mouth rinse • Pain control • Debridement to relieve soft tissue irritation and infection control	• By dentist
Stage 1	• Exposed and necrotic bone or fistulas that probe to bone in patients who are asymptomatic and have no evidence of infection		
Stage 2	• Exposed and necrotic bone or fistulas that probe to bone associated with • Infection as evidenced by pain and erythema in the region of exposed bone with or without purulent drainage	• Antibacterial mouth rinse • Antibiotic therapy and pain control • Surgical debridement or resection for longer-term palliation of infection and pain	• Seek expert guidance of an oral and maxillofacial surgeon (OMFS) or an oral oncology center with experience in the management of patients with MRONJ
Stage 3	• Exposed and necrotic bone or a fistula that probes to bone in patients with pain, infection, and one of the following: • Exposed and necrotic bone extending beyond the region of alveolar bone (i.e., inferior border and ramus in mandible, maxillary sinus, and zygoma in maxilla) • Resulting in pathologic fracture, extraoral fistula, oral antral or oral nasal communication, or osteolysis extending to inferior border of the mandible or sinus floor		• Refer the patient to an OMFS or an oral oncology center with experience in the management of patients with MRONJ
Regardless of MRONJ stage, mobile segments of bony sequestrum should be removed without exposing uninvolved bone. Extraction of symptomatic teeth within exposed necrotic bone should also be considered because it is unlikely that extraction will exacerbate the established necrotic process			

Source: Adapted from Ruggiero SL, Dodson TB, Fantasia J, et al. American Association of Oral and Maxillofacial Surgeons position paper on medication-related osteonecrosis of the jaw—2014 update. *J Oral Maxillofac Surg*. 2014;72(10):1938–1956.

- High and narrow palatal vault, severe malocclusions with maxillary retrognathy, and micrognathia and marked tooth crowding.
- Sleep apnea.

Ehlers–Danlos Syndrome

Ehlers–Danlos syndrome (EDS) is a highly heterogeneous group of disorders of collagen, with 10 different subtypes recognized associated with varying degrees of skin fragility, skin hyperextensibility, and joint hypermobility.[264]

- *Types I, II, and III*: autosomal dominant inheritance. The biochemical basis to these forms of EDS are yet to be determined.
- *Type IV* (vascular type): autosomal dominant. It involves the arteries, the bowel, and the uterus, as well as the skin. Mutations in the *COL3A1* gene produce abnormalities in the structure, synthesis, and secretion of Type III collagen.
- *Type VI*: inheritance is autosomal recessive.
- *Type VII*: an autosomal dominant disorder in which there is a defect in the conversion of procollagen to collagen; *COL1A1* and *COL1A2* mutations delete the N-proteinase cleavage sites.

There are also other rare forms of EDS.

Osteogenesis Imperfecta

Osteogenesis imperfecta (OI) is a heterogeneous group of mainly autosomally dominant inherited disorders.[265] There are four main types of OI (I–IV), with other clinical subtypes also described (V, VI, and VII). The major clinical feature is bone fragility, but other collagen-containing tissues are also involved, such as tendons, the skin, and the eyes, and of course the teeth, as dentinogenesis imperfecta.

- *Type I*: mild bony deformities, blue sclerae, defective dentine, early-onset deafness, hypermobility of joints, and heart valve disorders.
- *Type II*: perinatal death.
- *Type III*: severe bone deformity, blue sclerae.
- *Type IV*: fewer fractures, normal sclerae, normal lifespan.

Treatment involves bisphosphonates (particularly intravenous pamidronate), given from an early age, that is stopped at about 18–21 years with growth arrest, and this has considerably improved bone cortical thickness and skeletal development. Overall prognosis is still variable and dependent on the severity of the disease. To date no cases of ONJ with the use of bisphosphonates in this clinical setting have been reported.

Achondroplasia ("Dwarfism")

Achondroplasia is an autosomal dominant disease, but spontaneous mutations can also occur.[266] The condition is caused by a defect in the fibroblast growth factor receptor-3 gene. The trunk is of normal length, but the limbs are very short and broad due to abnormal endochondral ossification. The vault of the skull is enlarged, the face is small, and the nose bridge is flat. Intelligence is unaffected. Diagnosis is usually made by fetal ultrasound by progressive discordance between the femur length and the head circumference and diameter. Dental malocclusion is common.

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